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L78 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:674642 HCAPLUS

DN 137:210939

ED Entered STN: 06 Sep 2002

TI Methods of use of compounds which inhibit the **stem cell factor signaling pathway**

IN Longley, B. Jack

PA USA

SO U.S. Pat. Appl. Publ., 22 pp., Cont.-in-part of U.S. Ser. No. 306,143.

CODEN: USXXCO

DT Patent

LA English

IC ICM C12Q001-00

NCL 435004000

CC 1-7 (Pharmacology)

Section cross-reference(s): 2

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002123031	A1	20020905	US 1999-474478	19991229 <--
	US 6576812	B1	20030610	US 1999-306143	19990506 <--
	WO 2000067794	A1	20001116	WO 2000-US12405	20000505 <--
	W:			AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	
	RW:			GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG	
PRAI	US 1999-306143	A2	19990506	<--	
	US 1999-474478	A2	19991229		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2002123031	ICM	C12Q001-00

NCL 435004000
 US 2002123031 ECLA C07K016/28A <--
 US 6576812 ECLA C07K016/28A <--
 AB The invention provides a method of preventing or treating in a subject **contact dermatitis** which comprises administering to the subject an amount of a compound capable of inhibiting the **stem cell factor signaling pathway** effective to prevent or treat **contact dermatitis** so as to thereby prevent or treat **contact dermatitis** in the subject. The invention also provides a methods of preventing or treating in a subject **hyperpigmentation, asthma, cutaneous inflammation, anaphylaxis and bronchospasm, mastocytosis, tumors** which express activated kit, and conception.
 ST **stem cell factor signaling pathway inhibitor therapeutic; dermatitis hyperpigmentation asthma stem cell factor signaling pathway inhibitor; skin inflammation mastocytosis stem cell factor signaling pathway inhibitor; anaphylaxis bronchospasm tumor stem cell factor signaling pathway inhibitor; contraceptive stem cell factor signaling pathway inhibitor**
 IT Antibodies and Immunoglobulins
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (IgA; **stem cell factor signaling pathway inhibitors** for)
 IT Antibodies and Immunoglobulins
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (IgD; **stem cell factor signaling pathway inhibitors** for)
 IT Antibodies and Immunoglobulins
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (IgE; **stem cell factor signaling pathway inhibitors** for)
 IT Antibodies and Immunoglobulins
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (IgG; **stem cell factor signaling pathway inhibitors** for)
 IT Antibodies and Immunoglobulins
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (IgM; **stem cell factor signaling pathway inhibitors** for)
 IT Enzymes, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (SCF-cleaving; **stem cell factor signaling pathway inhibitors** for)
 IT Drug delivery systems
 (anal; **stem cell factor signaling pathway inhibitors** for)
 IT Ligands
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (binding; **stem cell factor signaling pathway inhibitors** for)
 IT **Dermatitis**
 (contact; **stem cell factor signaling pathway inhibitors** for)

IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(fusion products; **stem cell factor
signaling pathway** inhibitors for)

IT Digestive tract, **neoplasm**
(gastrointestinal stromal tumor, inhibitors; **stem
cell factor signaling pathway**
inhibitors for)

IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(humanized; **stem cell factor
signaling pathway** inhibitors for)

IT Skin, **disease**
(hyperpigmentation; **stem cell
factor signaling pathway** inhibitors for)

IT Allergy
(hypersensitivity; **stem cell
factor signaling pathway** inhibitors for)

IT Drug delivery systems
(injections, i.m.; **stem cell factor
signaling pathway** inhibitors for)

IT Drug delivery systems
(injections, i.p.; **stem cell factor
signaling pathway** inhibitors for)

IT Drug delivery systems
(injections, i.v.; **stem cell factor
signaling pathway** inhibitors for)

IT Drug delivery systems
(injections, s.c.; **stem cell factor
signaling pathway** inhibitors for)

IT Drug delivery systems
(intestinal; **stem cell factor
signaling pathway** inhibitors for)

IT Drug delivery systems
(intralesional; **stem cell factor
signaling pathway** inhibitors for)

IT Skin
(keratinocyte; **stem cell factor
signaling pathway** inhibitors for)

IT Dimerization
(kit; **stem cell factor
signaling pathway** inhibitors for)

IT Drug delivery systems
(liposomes; **stem cell factor
signaling pathway** inhibitors for)

IT Antibodies and Immunoglobulins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(monoclonal; **stem cell factor
signaling pathway** inhibitors for)

IT Drug delivery systems
(mucosal; **stem cell factor
signaling pathway** inhibitors for)

IT Drug delivery systems
(nasal; **stem cell factor
signaling pathway** inhibitors for)

IT Gamete and Germ cell
(neoplasm, inhibitors; **stem cell
factor signaling pathway** inhibitors for)

IT Mast cell
(neoplasm, mastocytoma; **stem cell**

factor signaling pathway inhibitors for)

IT Drug delivery systems
(ophthalmic; stem cell factor signaling pathway inhibitors for)

IT Drug delivery systems
(oral; stem cell factor signaling pathway inhibitors for)

IT Drug delivery systems
(otic; stem cell factor signaling pathway inhibitors for)

IT Bronchi, disease
(spasm; stem cell factor signaling pathway inhibitors for)

IT Allergy inhibitors
Anaphylaxis
Anti-inflammatory agents
Antiasthmatics
Antitumor agents
Asthma
Canis familiaris
Contraceptives
Dermatitis
Felis catus
Human
Mast cell
Melanocyte
Neoplasm
Peptidomimetics
Signal transduction, biological
Transformation, genetic
Urticaria
(stem cell factor signaling pathway inhibitors for)

IT Stem cell factor
Transgene
c-Kit (protein)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(stem cell factor signaling pathway inhibitors for)

IT Antibodies and Immunoglobulins
Nucleic acids
Organic compounds, biological studies
Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stem cell factor signaling pathway inhibitors for)

IT Drug delivery systems
(topical; stem cell factor signaling pathway inhibitors for)

IT 9004-06-2, Elastase 97501-92-3, Chymase 138359-29-2, Kit tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(stem cell factor signaling pathway inhibitors for)

IT 454746-24-8 454746-25-9 454746-26-0 454746-27-1
RL: PRP (Properties)
(unclaimed nucleotide sequence; methods of use of compds. which inhibit the stem cell factor signaling pathway)

DN 133:361913
 ED Entered STN: 21 Nov 2000
 TI Methods for inhibiting **cutaneous inflammation and hyperpigmentation**
 IN Longley, B. Jack
 PA The Trustees of Columbia University In the City of New York, USA
 SO PCT Int. Appl., 72 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K039-395
 ICS C07K016-00; C12Q001-70
 CC 15-3 (Immunochemistry)
 Section cross-reference(s): 2, 8, 62, 63

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067794	A1	20001116	WO 2000-US12405	20000505 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6576812	B1	20030610	US 1999-306143	19990506 <--
US 2002123031	A1	20020905	US 1999-474478	19991229 <--
PRAI US 1999-306143	A2	19990506 <--		
US 1999-474478	A2	19991229		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000067794	ICM	A61K039-395
	ICS	C07K016-00; C12Q001-70
US 6576812	ECLA	C07K016/28A <--
US 2002123031	ECLA	C07K016/28A <--

AB This invention provides a method of preventing or treating in a subject **contact dermatitis** which comprises administering to the subject an amount of a compound capable of inhibiting the **stem cell factor signaling pathway** effective to prevent or treat **contact dermatitis** so as to thereby prevent or treat **contact dermatitis** in the subject. This invention also provides a method of preventing or treating in a subject **hyperpigmentation, asthma, cutaneous inflammation, anaphylaxis and bronchospasm, mastocytosis, tumors** which express activated **kit**, and conception.

ST **contact dermatitis antiasthmatic**

IT antiallergic monoclonal ACK2

IT Keratins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(14, promoter of gene encoding; methods for inhibiting

cutaneous inflammation and hyperpigmentation

)

IT Immunoglobulins

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(A, anti-kit; methods for inhibiting **cutaneous inflammation and hyperpigmentation**)

IT Immunoglobulins

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(D, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Immunoglobulins

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(E, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Immunoglobulins

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(G, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Immunoglobulins

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(M, anti-kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Drug delivery systems

(anal; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Dermatitis

(contact; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Fats and Glyceridic oils, biological studies

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(croton; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Bladder

(cystitis, interstitial; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Skin

(epidermis, interadnexal; methods for inhibiting cutaneous inflammation and hyperpigmentation)
)

IT Neoplasm

(gastrointestinal stroma; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Skin, disease

(hyperpigmentation; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Allergy

(hypersensitivity; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Skin, disease

(hypopigmentation; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Drug delivery systems

(i.p.; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Respiratory tract

(inflammation; methods for inhibiting cutaneous inflammation and hyperpigmentation)

IT Drug delivery systems

(injections, i.m.; methods for inhibiting cutaneous inflammation and hyperpigmentation)

- IT Drug delivery systems
(injections, i.v.; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(injections, s.c.; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(intestinal; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(intralesional; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(intravesicular; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Abdomen
- Ear
(irritant application to murine; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(kit; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(liposomes; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Mast cell
(mastocytoma; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Allergy inhibitors
Anaphylaxis
Antiasthmatics
Asthma
Canidae
Carcinoma
Cat (Felis catus)
Contraceptives
Cosmetics
Dermatitis
Electron microscopy
Mammal (Mammalia)
Melanoma
Molecular weight distribution
Peptidomimetics
Signal transduction, biological
Sunburn
Urticaria
(methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Antibodies
Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Transgene
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(mice bearing; methods for inhibiting cutaneous

- inflammation and hyperpigmentation)**
- IT Antibodies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(monoclonal, anti-kit, ACK2; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(nasal; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Gamete and Germ cell
(neoplasm; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Promoter (genetic element)
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(of cytokeratin 14 gene; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(ophthalmic; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(oral; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(otic; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(parenterals; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Nose
(rhinitis; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Stem cell factor
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(signaling pathway; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT UV radiation
(skin injury from; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Olive oil
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Bronchi
(spasm; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Digestive tract
(stromal tumor; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(topical; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Mouse
(transgenic; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT Drug delivery systems
(transmucosal; methods for inhibiting cutaneous inflammation and hyperpigmentation)
- IT 9004-06-2, Elastase 97501-92-3, Chymase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(inhibitors; methods for inhibiting **cutaneous inflammation and hyperpigmentation**)

IT 70-34-8, Dinitrofluorobenzene

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(methods for inhibiting **cutaneous inflammation and hyperpigmentation**)

IT 67-64-1, Acetone; uses

RL: NUU (Other use, unclassified); USES (Uses)
(solvent; methods for inhibiting **cutaneous inflammation and hyperpigmentation**)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Bennett; US 5997865 A 1999 HCAPLUS

(2) Brownell; US 5911988 A 1999 HCAPLUS

(3) Ravetch; US 5877396 A 1999 HCAPLUS

L78 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:64924 HCAPLUS

DN 132:320348

ED Entered STN: 27 Jan 2000

TI Coexpression of c-kit and **stem cell**

factor in breast **cancer** results in enhanced sensitivity to members of the EGF family of growth factors

AU Hines, Susan J.; Litz, Julie S.; Krystal, Geoffrey W.

CS Department of Medicine, Medical College of Virginia and McGuire VA Medical Center, Richmond, VA, USA

SO Breast Cancer Research and Treatment (1999), 58(1), 1-10

CODEN: BCTRD6; ISSN: 0167-6806

PB Kluwer Academic Publishers

DT Journal

LA English

CC 14-1 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 2

AB **Kit**, a tyrosine kinase growth **factor** receptor, and its ligand, **stem cell factor (SCF)**,

are commonly coexpressed in breast **cancer**. We have previously shown that MCF7 cells (that naturally express **SCF**) transfected with a c-kit expression vector exhibit enhanced growth in serum-free medium supplemented with IGF-1. Consequently, we wished to examine the interaction of **Kit/SCF** with addnl. growth **factors** important in the biol. of breast **cancer**. MCF7 transfectants expressing **Kit**, cultured in serum-free medium supplemented with EGF, displayed more than twice the growth of controls at identical EGF concns. Similar responses were seen in the presence of heregulin α . The specificity of the **Kit**-mediated response was illustrated by a reduction in heregulin-stimulated growth in the presence of a monoclonal antibody directed against the **Kit** receptor. In addition, EGF-and heregulin-stimulated growth of the ZR75-1 cell line that naturally coexpresses **Kit** and **SCF** was also inhibited by the **Kit** blocking antibody. Preliminary investigations into the **signal transduction pathways** activated by these growth **factors** revealed that **SCF** activated both the Ras-MAP kinase and phosphatidyl-inositol-3-kinase (P13 kinase) **pathway**. Both EGF and heregulin activated MAPK but to a lesser degree than **SCF**, and combination of **SCF** with these growth **factors** resulted in enhanced MAPK activation. Assessment of P13K **pathway** activation using anti-phospho-Akt antibodies revealed that EGF was a poor activator of Akt; activation of this **pathway** was markedly enhanced by the addition of **SCF**.

Heregulin activated Akt and addition of SCF provided no further activation. Taken together these results suggest that coexpression of SCF and Kit may enhance responsiveness to erbb ligands by enhancing activation of the MAPK and P13K pathways.

- ST ckit **stem cell factor** breast **cancer**
EGF MAP kinase
- IT Cell proliferation
(c-kit and **stem cell factor**
coexpression in human breast **cancer** results in enhanced
sensitivity to members of the EGF family of growth factors)
- IT **Stem cell factor**
c-Kit (protein)
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence);
BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); OCCU (Occurrence); PROC (Process)
(c-kit and **stem cell factor**
coexpression in human breast **cancer** results in enhanced
sensitivity to members of the EGF family of growth factors)
- IT Mammary gland
(neoplasm; c-kit and **stem cell**
factor coexpression in human breast **cancer** results in
enhanced sensitivity to members of the EGF family of growth factors)
- IT Heregulins
RL: ADV (Adverse effect, including toxicity); BPR (Biological process);
BSU (Biological study, unclassified); BIOL (Biological study); PROC
(Process)
(α ; c- kit and **stem cell**
factor in breast **cancer** results in enhanced
sensitivity to members of the EGF family of growth factors)
- IT 62229-50-9, EGF
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence);
BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); OCCU (Occurrence); PROC (Process)
(c-kit and **stem cell factor**
coexpression in human breast **cancer** results in enhanced
sensitivity to members of the EGF family of growth factors)
- IT 115926-52-8, Phosphatidyl-inositol-3-kinase 142243-02-5, MAP kinase
148640-14-6, Akt kinase 149147-12-6, Akt kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(c-kit and **stem cell factor** in
breast **cancer** results in enhanced sensitivity to members of
the EGF family of growth factors)

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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L78 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1999:780242 HCAPLUS

DN 132:217164

ED Entered STN: 09 Dec 1999

TI **Stem cell factor/c-kit** system in spermatogenesis

AU Mauduit, Claire; Hamamah, Samir; Benahmed, Mohamed

CS INSERM U407, INSERM U407, Faculte de Medecine Lyon-Sud, Oullins, F-69921, Fr.

SO Human Reproduction Update (1999), 5(5), 535-545

CODEN: HRUPF8; ISSN: 1355-4786

PB Oxford University Press

DT Journal; General Review

LA English

CC 2-0 (Mammalian Hormones)

Section cross-reference(s): 14

AB A review, with 92 refs., reporting a large number of data, obtained essentially in animal models, that suggest an important role for the **SCF/c-kit** system in spermatogenesis and, as a corollary, its potential involvement in spermatogenic defects. One of the major unresolved questions with male infertility is the identification of the mol. origin of a great majority of the spermatogenetic arrests currently diagnosed as idiopathic male infertility. During the past years, several families of regulating factors have been implicated in spermatogenesis defects observed essentially in animal models. Among these factors are **signalling** mols., and particularly the **stem cell factor (SCF)/c-kit** system. The **SCF** and its receptor **c-kit** are an appropriate example to illustrate the role of **signalling** mols. in the physiol. and pathol. of spermatogenesis. The **SCF/c-kit** regulates primordial germ cell migration, proliferation and apoptosis during fetal gonadal development. The **SCF/c-kit** also regulates spermatogonia proliferation in the adult animal. In mutant mice, abnormalities of the **SCF/c-kit** gene expression, such as gene deletion, point mutation, alternative splicing defect, lead to different types of spermatogenesis alterations (e.g., decrease in primordial germ cell migration, decrease in spermatogonia proliferation). More recently, defects in **SCF/c-kit** gene expression

have also been shown in human testicular dysfunctions. Indeed, a reduction in **SCF/c-kit** expression has been evidenced in oligozoospermia/azoospermia associated with an increase in the germ cell apoptosis process. In addition, **c-kit** seems to be a good marker of seminoma testicular tumors.

- ST review **stem cell factor c kit**
protein spermatogenesis; male infertility **stem cell factor c kit** protein review; seminoma **stem cell factor c kit** protein review
- IT Embryo, animal
(fetus, development; **stem cell factor/c-kit** system in spermatogenesis in relation to)
- IT **Fertility**
(male, disorder; **stem cell factor/c-kit** system in spermatogenesis in relation to)
- IT Testis, neoplasm
(seminoma; **stem cell factor/c-kit** system in spermatogenesis in relation to)
- IT **Spermatogenesis**
Testis
(**stem cell factor/c-kit** system in spermatogenesis)
- IT **Stem cell factor**
c-Kit (protein)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**stem cell factor/c-kit** system in spermatogenesis)
- IT Apoptosis
Cell migration
Cell proliferation
Signal transduction, biological
Testis, disease
(**stem cell factor/c-kit** system in spermatogenesis in relation to)

RE.CNT 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L78 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1999:763362 HCAPLUS

DN 132:76859

ED Entered STN: 03 Dec 1999

TI Regulation of the melanoma cell adhesion molecule gene in melanoma: modulation of mRNA synthesis by cyclic adenosine monophosphate, phorbol ester, and **stem cell factor/ c-kit signaling**

AU Karlen, Stephane; Braathen, Lasse R.

CS Dermatological Clinic, University of Bern, Bern, Switz.

SO Journal of Investigative Dermatology (1999), 113(5), 711-719

CODEN: JIDEAE; ISSN: 0022-202X

PB Blackwell Science, Inc.

DT Journal

LA English

CC 14-1 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 3

AB The melanoma cell adhesion mol. was identified as a human melanoma-associated antigen that increases in expression as **tumors** increase in thickness and begin to acquire **metastatic** potential. Clin. and exptl. evidences suggest that the development of **metastatic** capacity might be the consequence of increased melanoma cell adhesion mol. expression. The mechanisms for upregulation of the melanoma cell adhesion mol. during melanoma progression are, however, still poorly understood. In this study, we show that melanoma cell adhesion mol. expression is tightly regulated at the transcriptional level. Using a combination of CAT reporter assays and semiquant. RT-PCR, we observed that cAMP significantly increases transcription of the melanoma cell adhesion mol. in **nonmetastatic** melanoma cells. In **metastatic** cells, transcription of the gene was constitutive and could not be further increased by cAMP. On the other hand, melanoma cell adhesion mol. promoter activity was impeded upon treatment with phorbol esters or in the presence of **stem cell factor**, a phenomenon which was protein kinase C-dependent. Promoter-deletion studies demonstrated that the first 196 nt of the melanoma cell adhesion mol. promoter region are sufficient to get full expression in **metastatic** melanoma cells. This fragment contains five binding sites for the transcription factor Sp1 and DNA mobility shift expts. showed direct binding of Sp1 to the promoter. In conclusion, our results indicate that Sp1 is sufficient to drive constitutive melanoma cell adhesion mol. expression in **metastatic** melanoma cells. In **nonmetastatic** cells, however, melanoma cell adhesion mol. expression is repressed and we speculate that **stem cell factor/ c-Kit signaling** might be responsible for the control of melanoma cell adhesion mol. synthesis, and thus, perhaps, of melanoma progression and metastasis.

ST melanoma cell adhesion mol gene regulation; cAMP **stem cell factor** MCAM mRNA melanoma

IT Cell adhesion molecules

RL: BSU (Biological study, unclassified); BIOL (Biological study) (MCAM (melanoma cell adhesion mol.); regulation of melanoma cell adhesion mol. gene in melanoma by modulation of mRNA synthesis by cAMP, phorbol ester, and **stem cell factor/ c-kit signaling**)

- IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified);
BIOL (Biological study); OCCU (Occurrence)
(MCAM; regulation of melanoma cell adhesion mol. gene in melanoma by
modulation of mRNA synthesis by cAMP, phorbol ester, and **stem
cell factor/ c-kit signaling**)
- IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(Sp1; regulation of melanoma cell adhesion mol. gene in melanoma by
modulation of mRNA synthesis by cAMP, phorbol ester, and **stem
cell factor/ c-kit signaling**)
- IT Transcriptional regulation
(activation; regulation of melanoma cell adhesion mol. gene in melanoma
by modulation of mRNA synthesis by cAMP, phorbol ester, and
**stem cell factor/ c-kit
signaling**)
- IT Melanoma
(metastasis; regulation of melanoma cell adhesion mol. gene in melanoma
by modulation of mRNA synthesis by cAMP, phorbol ester, and
**stem cell factor/ c-kit
signaling**)
- IT Melanoma
Signal transduction, biological
(regulation of melanoma cell adhesion mol. gene in melanoma by
modulation of mRNA synthesis by cAMP, phorbol ester, and **stem
cell factor/ c-kit signaling**)
- IT **Stem cell factor**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(regulation of melanoma cell adhesion mol. gene in melanoma by
modulation of mRNA synthesis by cAMP, phorbol ester, and **stem
cell factor/ c-kit signaling**)
- IT 141436-78-4, Protein kinase C
RL: BAC (Biological activity or effector, except adverse); BPR (Biological
process); BSU (Biological study, unclassified); BIOL (Biological study);
PROC (Process)
(regulation of melanoma cell adhesion mol. gene in melanoma by
modulation of mRNA synthesis by cAMP, phorbol ester, and **stem
cell factor/ c-kit signaling**)
- IT 60-92-4, CAMP
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(regulation of melanoma cell adhesion mol. gene in melanoma by
modulation of mRNA synthesis by cAMP, phorbol ester, and **stem
cell factor/ c-kit signaling**)

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L78 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:671830 HCAPLUS

DN 130:50592

ED Entered STN: 23 Oct 1998

TI Lck associates with and is activated by **Kit** in a small cell lung cancer cell line: inhibition of **SCF**-mediated growth by the Src family kinase inhibitor PP1

AU Krystal, Geoffrey W.; DeBerry, Candy S.; Linnekin, Diana; Litz, Julie

CS Department of Medicine, Division of Hematology/Oncology, McGuire Veterans Affairs Medical Center, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA, 23249, USA

SO Cancer Research (1998), 58(20), 4660-4666

CODEN: CNREAB; ISSN: 0008-5472

PB American Association for Cancer Research

DT Journal

LA English

CC 14-1 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 2

AB At least 70% of small cell lung cancers (SCLCs) express the **Kit** receptor tyrosine kinase and its ligand, **stem cell factor (SCF)**. In an effort to define the **signal transduction pathways** activated by **Kit** in SCLC, the authors focused on Src family kinases and, in particular, Lck, a Src-related tyrosine kinase that is expressed in hemopoietic cells and certain tumors, including SCLC. **SCF** treatment of the H526 cell line induced a phys. association between **Kit** and Lck that, in vitro, was dependent on phosphorylation of the juxtamembrane domain of **Kit**. Stimulation of **Kit** with recombinant **SCF** resulted in a rapid 3-6-fold increase in the specific activity of Lck, which was similar in magnitude to the activation of Lck resulting from the crosslinking of the T-cell receptor complex of Jurkat cells. Lck activity peaked by 5 min after **SCF** addition, and the elevated activity persisted for at least 30 min in the presence of **SCF**, with kinetics similar to the activation of mitogen-activated protein kinase. PP1, an inhibitor of Src family kinases with selectivity for Lck, completely inhibited **SCF**-mediated growth but had little effect on insulin-like growth factor-I-mediated growth. PP1

antagonized both **SCF**-mediated proliferation and inhibition of apoptosis. PP1 had no effect on **Kit** kinase activity but was shown to block total Lck activity by at least 90% by immune complex kinase assay. Low levels of Src, Hck, and Yes were also expressed in the H526 cell line; only Yes showed a consistent increase in specific activity, which was also inhibited by PP1 following **SCF** treatment. These data demonstrate that, in the H526 SCLC cell line, Lck and, possibly, Yes are downstream of **Kit** in a **signal transduction pathway**; the inhibition by PP1 of **SCF**-mediated proliferation and inhibition of apoptosis suggests that Src family kinases are intermediates in the **signaling pathways** that regulate these processes.

ST Lck **Kit** kinase **signal transduction lung cancer**

IT **Signal transduction, biological**

(Lck assoc. with and is activated by **Kit** after induction with **stem cell factor** in human small cell lung cancer cell line)

IT **c-Kit (protein)**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(Lck assoc. with and is activated by **Kit** after induction with **stem cell factor** in human small cell lung cancer cell line)

IT **Stem cell factor**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(Lck assoc. with and is activated by **Kit** after induction with **stem cell factor** in human small cell lung cancer cell line)

IT **Apoptosis**

(Lck kinase role in **stem cell factor**-mediated proliferation and inhibition of apoptosis in human small cell lung cancer cell line)

IT **Phosphoproteins**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(pp56lck; Lck assoc. with and is activated by **Kit** after induction with **stem cell factor** in human small cell lung cancer cell line)

IT **Phosphorylation, biological**

(receptor; Lck association with phosphorylated **Kit** after induction with **stem cell factor** in human small cell lung cancer cell line)

IT **Lung, neoplasm**

(small-cell carcinoma; Lck assoc. with and is activated by **Kit** after induction with **stem cell factor** in human small cell lung cancer cell line)

IT 141349-91-9, CYes kinase

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(Lck and Yes activation after induction with **stem cell factor** in human small cell lung cancer cell line)

IT 114051-78-4 138359-29-2, CKit kinase

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(Lck assoc. with and is activated by **Kit** after induction with **stem cell factor** in human small cell lung cancer cell line)

IT 67763-96-6, Insulin-like growth factor I
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (Lck kinase role in **stem cell factor**
 -mediated proliferation and inhibition of apoptosis in human small cell lung **cancer** cell line in relation to)

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L78 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:651709 HCAPLUS

DN 130:24049

ED Entered STN: 15 Oct 1998

TI **Stem cell factor** augments

FcεRI-mediated TNF-α production and stimulates MAP kinases
 via a different **pathway** in MC/9 mast cells

AU Ishizuka, Tamotsu; Kawasome, Hideki; Terada, Naohiro; Takeda, Katsuyuki;
 Gerwins, Par; Keller, Gordon M.; Johnson, Gary L.; Gelfan, Erwin W.

CS Division of Basic Sciences, Dep. of Pediatrics, National Jewish Medical
 and Research Center, Denver, CO, 80206, USA

SO Journal of Immunology (1998), 161(7), 3624-3630

CODEN: JOIMA3; ISSN: 0022-1767

PB American Association of Immunologists

DT Journal

LA English

CC 15-9 (Immunochemistry)

AB Mast cells express the receptor tyrosine kinase **kit/stem**
cell factor receptor (SCFR) which is encoded by the
 proto-oncogene **c-kit**. Ligation of SCFR induces its dimerization
 and activation of its intrinsic tyrosine kinase activity leading to

activation of Raf-1, phospholipases, phosphatidylinositol 3-kinase, and extracellular **signal**-regulated kinases. However, little is known about the downstream **signals** initiated by SCFR ligation except for activation of extracellular **signal**-regulated kinases. The murine and mast cell line, MC/9, synthesizes and secretes TNF- α following the aggregation of high affinity Fc receptors for IgE (Fc ϵ RI). Ligation of SCFR or Fc ϵ RI on MC/9 cells resulted in the activation of all 3 MAP kinase family members, extracellular **signal**-regulated kinases, c-Jun N-terminal kinase (JNK), and p38.

Stem cell factor (SCF)-induced

activation of JNK and p38 was insensitive to wortmannin, cyclosporin A, and FK506 whereas activation of these kinases through Fc ϵ RI was sensitive to these drugs. Coligation of SCFR augmented Fc ϵ RI-mediated activation of MAP kinases, especially JNK activation, and SCF augmented Fc ϵ RI-mediated TNF- α production in MC/9 cells, although SCF alone did not induce TNF- α production. This augmentation by SCF was regulated at the level of transcription, at least in part, since the promoter activity of TNF- α was enhanced following addition of SCF. Thus, SCF can augment Fc ϵ RI-mediated JNK activation and cytokine gene transcription but via **pathways** that are regulated differently than the ones activated through Fc ϵ RI.

- ST **stem cell factor** Fc ϵ RI TNF MAP kinase
mast cell; **tumor** necrosis factor mast cell **stem**
cell factor Fc ϵ RI
- IT Immunoglobulin receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(IgE type I; **stem cell factor** augments
Fc ϵ RI-mediated TNF- α production and stimulates MAP kinases
via a different **pathway** in MC/9 mast cells)
- IT **Tumor** necrosis factors
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**stem cell factor** augments
Fc ϵ RI-mediated TNF- α formation and stimulates MAP kinases
via different **pathway** in MC/9 mast cells)
- IT Mast cell
Signal transduction, biological
(**stem cell factor** augments
Fc ϵ RI-mediated TNF- α production and stimulates MAP kinases
via a different **pathway** in MC/9 mast cells)
- IT **Stem cell factor**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**stem cell factor** augments
Fc ϵ RI-mediated TNF- α production and stimulates MAP kinases
via a different **pathway** in MC/9 mast cells)
- IT 137632-08-7, Erk2 kinase 137632-08-7 155215-87-5, JNK kinase
165245-96-5, p38 Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**stem cell factor** augments
Fc ϵ RI-mediated TNF- α production and stimulates MAP kinases
via a different **pathway** in MC/9 mast cells)

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L78 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:312127 HCAPLUS

DN 129:93896

ED Entered STN: 28 May 1998

TI Murine **cutaneous mastocytosis** and **epidermal melanocytosis** induced by keratinocyte expression of transgenic **stem cell factor**

AU Kunisada, Takahiro; Lu, Shu-Zhuang; Yoshida, Hisahiro; Nishikawa, Satomi; Nishikawa, Shin-Ichi; Mizoguchi, Masako; Hayashi, Shin-Ichi; Tyrrell, Lynda; Williams, David A.; Wang, Xiaomei; **Longley, B. Jack**

CS Department of Immunology, School of Life Science, Faculty of Medicine, Tottori University, Yonago, 683, Japan

SO Journal of Experimental Medicine (1998), 187(10), 1565-1573
CODEN: JEMEAU; ISSN: 0022-1007

PB Rockefeller University Press

DT Journal

LA English

CC 14-9 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 2, 15

AB The growth and differentiation of mast cells and melanocytes require **stem cell factor (SCF)**, the ligand for the **kit** receptor tyrosine kinase. **SCF** may exist as a membrane-bound or soluble mol. Abnormalities of the **SCF-kit signaling pathway**, with increased local

concns. of soluble **SCF**, have been implicated in the pathogenesis of the human disease **cutaneous mastocytosis**, but have not yet been shown to play a causal role. To investigate both the potential of **SCF** to cause **mastocytosis** and its role in **epidermal** melanocyte homeostasis, we targeted the expression of **SCF** to **epidermal** keratinocytes in mice with two different transgenes controlled by the human keratin 14 promoter. The transgenes contained cDNAs that either produced **SCF**, which can exist in both membrane-bound and soluble forms, or **SCF**, which remains essentially membrane bound. Murine **epidermal** keratinocyte expression of membrane-bound/soluble **SCF** reproduced the phenotype of human **cutaneous mastocytosis**, with **dermal** mast cell infiltrates and **epidermal hyperpigmentation**, and caused the maintenance of a population of melanocytes in the interadnexal **epidermis**, an area where melanocytes and melanin are found in human **skin** but where they are not typically found in murine **skin**. Expression of membrane-bound **SCF** alone resulted in **epidermal** melanocytosis and melanin production, but did not by itself cause **mastocytosis**. We conclude, first, that a phenotype matching that of human **mastocytosis** can be produced in mice by keratinocyte overprodn. of soluble **SCF**, suggesting a potential cause of this disease. Second, we conclude that keratinocyte expression of membrane-bound **SCF** results in the postnatal maintenance of **epidermal** melanocytes in mice. Since the resulting animals have **skin** that more closely approximates human **skin** than do normal mice, their study may be more relevant to human melanocyte biol. than the study of **skin** of normal mice.

- ST **mastocytosis melanocyte stem cell**
- IT **factor keratinocyte**
- IT **Skin**
 - (**epidermis**; expression of **stem cell factor** by keratinocyte induce murine **cutaneous mastocytosis** and **epidermal** melanocytosis)
- IT Cell differentiation
 - Melanocyte
 - Mouse
 - (expression of **stem cell factor** by keratinocyte induce murine **cutaneous mastocytosis** and **epidermal** melanocytosis)
- IT **Stem cell factor**
 - RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (expression of **stem cell factor** by keratinocyte induce murine **cutaneous mastocytosis** and **epidermal** melanocytosis)
- IT c-Kit (protein)
 - RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (expression of **stem cell factor** by keratinocyte induce murine **cutaneous mastocytosis** and **epidermal** melanocytosis)
- IT **Skin, disease**
 - (**hyperpigmentation**; expression of **stem cell factor** by keratinocyte induce murine **cutaneous mastocytosis** and **epidermal** melanocytosis)
- IT **Skin**
 - (keratinocyte; expression of **stem cell factor** by keratinocyte induce murine **cutaneous mastocytosis** and **epidermal** melanocytosis)
- IT Mast cell
 - (mastocytoma; expression of **stem cell factor** by keratinocyte induce murine **cutaneous mastocytosis** and **epidermal** melanocytosis)

IT Cell migration

(of melanocyte; expression of **stem cell factor** by keratinocyte induce murine cutaneous mastocytosis and epidermal melanocytosis)

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L78 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1992:149933 HCAPLUS

DN 116:149933

ED Entered STN: 17 Apr 1992

TI The c-kit receptor ligand functions as a mast cell chemoattractant

AU Meininger, Cynthia J.; Yano, Hiroshi; Rottapel, Robert; Bernstein, Alan; Zsebo, Krisztina M.; Zetter, Bruce R.

CS Dep. Surg., Harvard Med. Sch., Boston, MA, 02115, USA

SO Blood (1992), 79(4), 958-63
 CODEN: BLOOAW; ISSN: 0006-4971
 DT Journal
 LA English
 CC 15-9 (Immunochemistry)
 Section cross-reference(s): 2
 AB Mast cells accumulate at sites of neovascularization, solid tumors, and many immune reactions. Such accumulation requires directed migration of mature mast cells or their precursors. The nature of the chemoattractants that regulate mast cell motility and the identity of the receptors that mediate the chemotactic response are poorly understood. The ability was tested of **stem cell factor** (**SCF**), a mast cell growth factor, to stimulate mast cell migration. The results show that **SCF** is a potent mast cell attractant that stimulates directional motility of both mucosal and connective tissue-type mast cells. The activity is potentiated by costimulation with interleukin-3 (IL-3), another mast cell chemoattractant. **SCF**, a known ligand for the **c-kit** tyrosine kinase receptor, did not stimulate motility in W42 mutant mast cells, which have a defective **c-kit** tyrosine kinase. However, W42 mast cells still migrated in response to IL-3. Thus, **SCF** is a chemotactic factor as well as a growth factor and the **c-kit** receptor can transduce **signals** leading to both cell proliferation and increased directional cell motility.
 ST **stem cell factor** mast cell chemotaxis
 IT **Signal transduction, biological**
 (of chemotactic mobility of mast cells, **stem cell factor** receptors in)
 IT Chemotaxis
 (of mast cells, **stem cell factor** induction of)
 IT Mast cell
 (**stem cell factor** as chemoattractant for)
 IT Receptors
 RL: BIOL (Biological study)
 (hematopoietic cell growth factor KL, ligand binding to, mast cell chemotaxis by)
 IT **Hemopoietins**
 RL: BIOL (Biological study)
 (**hematopoietic cell growth factors** KL, receptors, ligand binding to, mast cell chemotaxis by)
 IT Lymphokines and Cytokines
 RL: BIOL (Biological study)
 (interleukin 3, **stem cell factor**-induced chemotaxis of mast cell enhancement by)

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L93 ANSWER 1 OF 3 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
 AN 2003-332673 [31] WPIX
 CR 2003-201461 [19]; 2003-201462 [19]; 2003-201519 [19]; 2003-201520 [19];
 2003-210306 [20]; 2003-221442 [21]; 2003-221443 [21]; 2003-221534 [21];
 2003-312615 [30]; 2003-371772 [35]; 2003-430378 [40]; 2003-457306 [43]
 DNC C2003-086128
 TI Use of tyrosine kinase inhibitor for treating allergic diseases e.g.
 asthma.
 DC B03 C02
 IN KINET, J; MOUSSY, A
 PA (ABSC-N) AB SCI
 CYC 101
 PI WO 2003002106 A2 20030109 (200331)* EN 42 A61K031-00
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
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 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
 RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
 ZW
 EP 1401413 A2 20040331 (200424) EN A61K031-00
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 ADT WO 2003002106 A2 WO 2002-IB3297 20020628; EP 1401413 A2 EP 2002-755512
 20020628, WO 2002-IB3297 20020628
 FDT EP 1401413 A2 Based on WO 2003002106
 PRAI US 2001-301408P 20010629
 IC ICM A61K031-00
 ICS A61K031-404; A61K031-505; A61K031-506; A61K031-517; A61K031-519
 AB WO2003002106 A UPAB: 20040408
 NOVELTY - Treatment of allergic diseases involves administration of a
 tyrosine kinase inhibitor (I) (preferably c-kit inhibitor (Ia)).
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
 following:
 (1) treating allergic diseases by administration of activated (Ia)
 obtainable by screening methods (M1) involves:
 (i) (a1) contacting activated c-kit (preferably **stem**
cell factor activated c-kit wild) and at least one
 compound to be tested to form a complex;
 (ii) (a2) testing and selecting a subset of compounds (c1) inhibiting
 activated c-kit where the cells are interleukin-3 (IL-3) dependent cells
 cultured in presence IL-3, to identify a subset of candidate compounds
 targeting specifically c-kit;
 (2) treating allergic diseases by administration of activated (Ia)
 obtainable by screening method (M2) comprising:
 (a) performing a proliferation assay with cells expressing a mutant

c-kit (e.g. in the transphosphorylase domain), with test compounds to identify (c1) targeting activated c-kit by measuring the extent of cell death where the mutant c-kit is a permanent activated c-kit;

(b) performing a proliferation assay with cells expressing c-kit wild, with (c1) identified in (a), where the cells are IL-3 dependent cells cultured in presence of IL-3, to identify a subset of candidate compounds targeting specifically c-kit; and

(c) performing a proliferation assay with cells expressing c-kit, with (c1) identified in (b) and selecting (c1) targeting c-kit wild, by measuring the extent of cell death where (c1) have IC50 less than 10 μ M (preferably less than 1 μ M);

(3) use of (Ia) in the manufacture of a medicament for treating allergic diseases;

(4) a composition (A1) for intranasal or topical administration with an aerosolized formulation to target respiratory tract comprising (I);

(5) an aerosol device preferably with metered dose valve, comprising (A1); and

(6) a nasal dropper or spray device comprising (I) (preferably (Ia)).

ACTIVITY - Antiallergic; Antiasthmatic; Antiinflammatory; Immunosuppressive; Dermatological; Antiparasitic. Passive cutaneous anaphylaxis in mice was treated with 4-(4-Methylpiperazine-1-ylmethyl)-N-(4-methyl-3-(4-pyridine-3-yl)pyrimidine-2-ylamino)phenyl)-benzamide (Ib). Mice were administered with (Ib) everyday for 1 week prior antigen challenge at the dosage of 2 mg/day. After a week mice were anesthetized and injected with immunoglobulin E (IgE) (20 ng/20 μ l) and phosphate buffered saline (PBS) in the right and left ears respectively. After 24 hours Evans blue (1%, 100 μ l) containing dinitrophenyl-albumin (100 μ g) were injected in tail vein of mice. Mice were sacrificed after 90 minutes. The ears were cut off and incubated in formamide (1 ml) for 48 hours at 54 deg. C. The results showed that in test animals released prostaglandin 1 and were in good health than the control treated with vehicle.

MECHANISM OF ACTION - Mast cell proliferation inhibitor; Tyrosine kinase inhibitor.

USE - For preventing, delaying and/or treating allergic diseases including asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic **contact dermatitis**, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation and blood sucking parasitic infestation in human, dogs and cats (especially blood sucking parasitic infestation in dogs and cats) (all claimed).

ADVANTAGE - The compounds are potent, non-toxic and selective c-kit wild inhibitor. The treatment is an alternative to the prior art, giving long term effectiveness and tolerance particularly on repeated administration. The selectivity of (I) (preferably (Ia) for its inability to promote death in IL-3 dependent cells cultured in presence of IL-3 gives stability in genetic transfer and hence permits screening efficiently.

Dwg.0/5

FS

CPI

FA

AB; GI; DCN

MC

CPI: B04-F02; B07-D12; B11-C03; B11-C04; B11-C08E; B12-K04; B12-M01A; B14-B02; B14-D06; B14-G02A; B14-K01A; B14-N04; **B14-N17**; **B14-N17C**; C04-F02; C07-D12; C11-C03; C11-C04; C11-C08E; C12-K04; C12-M01A; C14-B02; C14-D06; C14-G02A; C14-K01A; C14-N04; **C14-N17**; **C14-N17C**

TECH

UPTX: 20030516

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: (A1) is an aqueous and/or an ethanolic solution, a saline solution, colloidal suspension or microcrystalline suspension.

Preferred Device: The aerosol device has a liquid gas system, a suspension aerosol or a pressurized gas system.

Preferred Methods: (M1) further involves testing and selecting (c1) identified in (i). (c1) are inhibitors of mutant activated c-kit and are also capable of inhibiting **stem cell factor (SCF)**- activated c-kit wild. The putative inhibitors are tested in (i) and (ii) at a concentration above 10µM and below 1µM respectively. The culture media of IL-3 dependent cells comprises (ng/ml) of IL-3 (0.5 - 10, preferably 1 - 5). The extent of inhibition by (c1) is measured in vivo or in vitro using standard biochemical techniques such as immunoprecipitation and western blot in terms of the amount of c-kit phosphorylation. In (M2) the extent of cell death is measured by ³H-thymidine incorporation, the trypan blue exclusion method or flow cytometry with propidium iodide.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - (I) is selected from the group of N-phenyl-2-pyrimidine-amine derivatives of formula (II).

R1 - R3 = H, F, I, Br, Cl, 1-5C alkyl or (hetero)cyclic group (preferably a pyridyl group);

R4 - R6 = H, F, I, Br, Cl or 1-5C alkyl (preferably methyl); and

R7 = optionally substituted phenyl (preferably 1-benzyl-4-methyl piperazine).

The inhibitor is indolinone, pyrimidine derivative, pyrrolopyrimidine derivative, quinazoline derivative, quinoxaline derivative, pyrazole derivative, bis monocyclic, bicyclic or heterocyclic aryl compound, vinylene-azaindole derivative, pyridyl-quinolones derivative, styryl compound, styryl-substituted pyridyl compound, seleoindole, selenide, tricyclic polyhydroxylic compound or benzylphosphonic acid compound (preferably N-phenyl-2-pyrimidine-amine derivatives, pyrrol-substituted indolinone, monocyclic, bicyclic aryl and heteroaryl compounds or quinazoline derivative).

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The IL-3 dependent cells are mast cells, transfected mast cells, BaF3 or IC-2.

ABEX

UPTX: 20030516

SPECIFIC COMPOUNDS - 4-(4-Methylpiperazine-1-ylmethyl)-N-(4-methyl-3-(4-pyridine-3-yl)pyrimidine-2-ylamino)phenyl)-benzamide (Ib) is specifically claimed as (I).

ADMINISTRATION - (I) is administered by topical, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, enteral, sublingual, intranasal or rectal routes (claimed).

L93 ANSWER 2 OF 3 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-201519 [19] WPIX

CR 2003-201461 [19]; 2003-201462 [19]; 2003-201520 [19]; 2003-210306 [20]; 2003-221442 [21]; 2003-221443 [21]; 2003-221534 [21]; 2003-312615 [30]; 2003-332673 [31]; 2003-371772 [35]; 2003-430378 [40]; 2003-457306 [43]

DNN N2003-160505 DNC C2003-051344

TI Identifying compounds that specifically deplete mast cells, useful for treating disorders such as autoimmune, CNS and inflammatory diseases, allergy, arthritis, bone loss, tumor angiogenesis, and infectious diseases.

DC B04 D16 S03

IN KINET, J; MOUSSY, A

PA (KINE-I) KINET J; (MOUS-I) MOUSSY A; (ABSC-N) AB SCI

CYC 101

PI WO 2003003004 A2 20030109 (200319)* EN 43 G01N033-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

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KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM

ZW

US 2003091974 A1 20030515 (200335) C12Q001-00
 EP 1434990 A2 20040707 (200444) EN G01N033-50
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR

ADT WO 2003003004 A2 WO 2002-IB3294 20020628; US 2003091974 A1 Provisional US
 2001-301404P 20010629, Provisional US 2001-301405P 20010629, Provisional
 US 2001-301406P 20010629, Provisional US 2001-301407P 20010629,
 Provisional US 2001-301408P 20010629, Provisional US 2001-301409P
 20010629, Provisional US 2001-301410P 20010629, Provisional US
 2001-301411P 20010629, Provisional US 2001-323313P 20010920, Provisional
 US 2001-323314P 20010920, Provisional US 2001-323315P 20010920, US
 2001-22842 20011220; EP 1434990 A2 EP 2002-755509 20020628, WO 2002-IB3294
 20020628

FDT EP 1434990 A2 Based on WO 2003003004

PRAI US 2001-22842 20011220; US 2001-301404P 20010629;
 US 2001-301405P 20010629; US 2001-301406P 20010629;
 US 2001-301407P 20010629; US 2001-301408P 20010629;
 US 2001-301409P 20010629; US 2001-301410P 20010629;
 US 2001-301411P 20010629; US 2001-323313P 20010920;
 US 2001-323314P 20010920; US 2001-323315P 20010920

IC ICM C12Q001-00; G01N033-00; G01N033-50
 ICS G01N033-567

AB WO2003003004 A UPAB: 20040712

NOVELTY - Identifying (M1) compounds capable of depleting mast cells, is new.

DETAILED DESCRIPTION - (M1) comprises:

- (a) culturing mast cells in vitro in a suitable culture medium;
- (b) adding to the culture medium at least one candidate compound to be tested;
- (c) measuring the extent to which the compounds promote mast cells death or interfere with, or inhibit mast cells growth and selecting compounds for which mast cells depletion is observed; and
- (d) identifying a subset of compounds that are unable to promote significant death of a cell, is new.

The compounds are non-toxic for other hematopoietic cells that are not mast cells or related cells or cell lines or derived cell lines, such as SCF independent expanded human normal CD34+ cells. Step (b) further comprises incubating the cells for prolonged period of time. (M1) alternatively comprises:

- (A) providing a culture of mast cells that are wild type mast cells, cell lines derived, activated mutant mast cell lines, or activated wild type mast cells and cell lines derived from it;
- (B) contacting the culture of the cells with at least one candidate compound allowing growth and/or survival of mast cells, measuring the level of cell death in the presence of the candidate compound, and comparing the level of cell death in the presence of the candidate compound to the level of cell death in the absence of the compound, where an increase in the level of cell death in the presence of the compound indicates mass cell depletion ability of the candidate compound;
- (C) providing a culture of at least one cell other than mast cells that are hematopoietic cells; and
- (D) contacting the culture of the cells with at least one compound identified allowing growth and/or survival of the cell, measuring the level of cell death in the presence of the compound, and comparing the level in the absence of the compound, where no significant increase indicates mass cells depletion specificity of the compound versus at least one another hematopoietic cell.

INDEPENDENT CLAIMS are also included for:

- (1) a compound obtainable by (M1), where the compound is capable of depleting mast cells and has no significant toxicity for other hematopoietic cells, preferably compounds having an E/S ratio ranging 1/1000 to 1/5;

(2) treating (M2) a disease such as autoimmune diseases, allergy, bone loss, tumor angiogenesis, inflammatory diseases, inflammatory bowel diseases, interstitial cystitis, mastocytosis, infectious diseases and CNS disorders, comprising administering a compound obtainable from (M1); and

(3) promoting (M3) hair growth and hair color revival, comprising administering a compound obtainable from (M1).

ACTIVITY - Neuroprotective; Antipsoriatic; Antiinflammatory; Antiulcer; Antirheumatic; Antiarthritic; Dermatological; Immunosuppressive; Nephrotropic; Hepatotropic; Antiasthmatic; Antiallergic; Cytostatic; Osteopathic; Antibacterial.

No biological data given.

MECHANISM OF ACTION - CD34-Agonist.

USE - The compound is useful to manufacture a medicament for treating disorders such as multiple sclerosis, psoriasis, intestine inflammatory disease, ulcerative colitis, Crohn's disease, rheumatoid arthritis, polyarthrititis, local and systemic scleroderma, systemic lupus erythematosus, discoid lupus erythematosus, cutaneous lupus, dermatomyositis, polymyositis, Sjogren's syndrome, nodular panarteritis, autoimmune enteropathy, proliferative glomerulonephritis, vasculitis, active chronic hepatitis and chronic fatigue syndrome, graft-versus-host disease, graft rejection in any organ transplantation including kidney, pancreas, liver, heart, lung and bone marrow, asthma, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite inflammation, blood sucking parasitic infestation, tumor angiogenesis, mastocytosis, mast cell leukemia, mucositis, interstitial cystitis, osteoporosis, Paget's disease and bacterial infections such as Gram-negative enterobacteria including E. coli, Klebsiella pneumoniae, Serratia marcescens, Citrobacter freundii and Salmonella typhimurium (all claimed).

Dwg. 0/0

FS CPI EPI

FA AB; DCN

MC CPI: B04-F04; B11-C08E1; B12-K04E; B14-A01; B14-C03; B14-C09B; B14-E10C; B14-E11; B14-G02C; B14-G02D; B14-H01; B14-K01A; B14-L01; B14-N04; B14-N12; B14-N17; B14-N17C; B14-S01; D05-H08; D05-H09

EPI: S03-E04D; S03-E14H

TECH UPTX: 20030320

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The mast cells in the method of identifying compounds capable of depleting mast cells are isolated mast cells and cell lines derived from it, BaF3, IC-2 mouse cells, HMC-1, P815 available at American Type Culture Collection (ATCC) under accession no. TIB-64, 10P2 under accession no. CRL-2034, 10P12 under accession no. CRL-2036, 11P0-1 under accession no. CRL-2037 and their derived cell lines. Other hematopoietic cells that are not mast cells or related cells or cell lines are human T lymphocyte Jurkat cell line (ATCC no. TIB-152), human B lymphocyte Daudi or Raji cell line (ATCC no. CCL-213 and CCL-86, respectively), the human monocytic U 937 cell line (ATCC no. CRL-1593.2) and the human HL-60 cell line (ATCC no. CCL-240, cell lines derived with ATCC no. CRL-2258 and CRL-2392) and normal human CD34+ cells that are expanded in a culture medium comprising a cocktail of cytokine except SCF. The compounds capable of depleting specifically mast cells at a concentration below 10 μ M, preferably below 1 μ M, are selected. The compounds exhibiting Ratios E/S from 1/1000 to 1/5, are selected. The cell death assay further comprises a cell proliferation assay, a cell viability assay and/or an apoptosis assay. The extent of cell death is measured by 3H thymidine incorporation, the trypan blue exclusion method, using propidium iodide or by the 51Cr-release assay. The extent of cell death is determined by a test of intracellular esterase activity, and a test of plasma membrane integrity, preferably using fluorescent calcein and ethidium homodimer-1, or by discriminating between

living and dead cells using DiOC18 and propidium iodide, or is measured by fluorometric assays of cell viability and cytotoxicity using a fluorescence microscope, a fluorometer, a fluorescence microplate reader or a flow cytometer. The mast cells that are IL-3 dependent cells are cultured in a culture media comprising IL-3 at a concentration comprised between 0.5-10 ng/ml, preferably 1-5 ng/ml. The compounds are indolinone, pyrimidine derivatives, pyrrolopyrimidine derivatives, quinazolone derivatives, quinoxaline derivatives, pyrazoles derivatives, bis monocyclic, bicyclic or heterocyclic aryl compounds, vinylene-azaindole derivatives and pyridyl-quinolones derivatives, styryl compounds, styryl-substituted pyridyl compounds, seleoindoles, selenides, tricyclic polyhydroxylic compounds or benzylphosphonic acid compounds. (M3) further comprises administering at least one antibiotic, preferably dapsone, azathioprine, erythromycin, propionylerythromycin, neomycin, gentamycin, tobramycin and mechlocycline, bacitracin, cephalosporins, aminoglycosides, tetracyclines, streptomycins.

ABEX UPTX: 20030320

ADMINISTRATION - The route of administration of the compound is via aerolized formulations to target areas of a patient's respiratory tract, or via the intranasal or topical routes (claimed).
No dosage given.

EXAMPLE - No suitable example given.

L93 ANSWER 3 OF 3 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2000-687622 [67] WPIX

DNC C2000-209364

TI Prevention and treatment of **contact dermatitis**, hyperpigmentation, cutaneous inflammation and other conditions, comprises inhibiting the **stem cell factor signaling** pathway.

DC B04 D16 D21

IN LONGLEY, B J

PA (UYCO) UNIV COLUMBIA NEW YORK; (LONG-I) LONGLEY B J

CYC 90

PI WO 2000067794 A1 20001116 (200067)* EN 72 A61K039-395
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW
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TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000048253 A 20001121 (200112) A61K039-395

US 2002123031 A1 20020905 (200260) C12Q001-00

US 6576812 B1 20030610 (200340) G01N033-00

ADT WO 2000067794 A1 WO 2000-US12405 20000505; AU 2000048253 A AU 2000-48253 20000505; US 2002123031 A1 CIP of US 1999-306143 19990506, US 1999-474478 19991229; US 6576812 B1 US 1999-306143 19990506

FDT AU 2000048253 A Based on WO 2000067794

PRAI US 1999-474478 19991229; US 1999-306143 19990506

IC ICM A61K039-395; C12Q001-00; G01N033-00

ICS A01K067-00; A01K067-027; A01K067-033; C07K016-00; C12Q001-70

AB WO 200067794 A UPAB: 20001223

NOVELTY - Preventing or treating diseases comprises administering a compound capable of inhibiting the **stem cell factor signaling** pathway.

DETAILED DESCRIPTION - Preventing or treating **contact dermatitis**, hyperpigmentation, asthma, cutaneous inflammation, anaphylaxis or bronchospasm, mastocytosis, urticaria, hypersensitivity, airway inflammation, interstitial cystitis or a tumor which expresses activated kit comprises administering to the subject a compound capable of inhibiting the **stem cell factor signaling** pathway effective to prevent or treat the conditions.

INDEPENDENT CLAIMS are also included for the following:

(1) providing contraception comprising administering a compound capable of inhibiting the cell factor **signaling** pathway effective to prevent conception;

(2) desensitizing a subject to an agent comprising administering to the subject, during the afferent phase of an immune response, a compound capable of inhibiting the **stem cell factor signaling** pathway effective to desensitize the subject;

(3) identifying a composition, compound or procedure which can produce a skin response comprising administering the compound or composition or applying the procedure to transgenic mice which express endogenous epidermal **stem cell factor** and analyzing the skin of the transgenic mice for a response;

(4) identifying a composition, compound or procedure which can reduce skin response in a subject comprises administering the composition or compound or applying the procedure to the transgenic mice which express endogenous epidermal **stem cell factor** and which had been induced to produce a skin disease and analyzing the skin to determine the reduction of the skin response;

(5) identifying a compound, composition or procedure which can reduce radiation damage to skin comprises administering the composition or compound or applying the procedure to the skin of the transgenic mice which express endogenous epidermal **stem cell factor**, subjecting the skin of the transgenic mice and control mice to radiation and analyzing the effects of the composition, compound or procedure on reducing skin radiation damage;

(6) a composition for treating human skin diseases comprising a compound that can treat skin diseases of the transgenic mice which express endogenous epidermal **stem cell factor** and a carrier, wherein the compound specifically targets the epidermal **stem cell factor** or its receptor.

ACTIVITY - Dermatological; antiinflammatory; antiasthmatic; antiinflammatory; antiallergic; immunosuppressive; cytostatic. No biological data is given.

MECHANISM OF ACTION - **Stem cell factor signaling** pathway inhibitor.

USE - The methods can be used to treat and/or prevent **contact dermatitis**, hyperpigmentation, asthma, cutaneous inflammation, anaphylaxis or bronchospasm, mastocytosis, urticaria, hypersensitivity, airway inflammation e.g. rhinitis, interstitial cystitis, a tumor which expresses activated kit wherein the tumor is e.g. a gastrointestinal stromal tumor or a germ cell tumor or radiation damage. The method may also be used to provide contraception (claimed).

Dwg.0/13

FS CPI

FA AB; DCN

MC CPI: B04-E01; B04-G01; B04-G21; **B04-H16**; **B04-M01**;
B04-N04; B11-C08E2; B12-K04E; B14-C03; B14-H01; B14-K01; B14-K01A;
B14-N07B; **B14-N17**; **B14-N17C**; B14-P01; B14-S06;
D05-H09; D05-H11A; D05-H12; D05-H16A

TECH UPTX: 20001223

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Methods: The methods comprise inhibiting the kinase enzymatic reaction of kit protein, inhibiting chymase, elastase or other **SCF** cleaving enzymes, inhibiting ligand binding with an antibody, peptide or nonpeptide chemical, inhibiting kit dimerization with an antibody, peptide or nonpeptide chemical, inhibiting downstream **signaling** of the kit activation pathway by blocking substrate association with the kit kinase domain, inhibiting downstream **signaling** of the kit activation pathway by blocking enzymatic function in the downstream **signaling** pathway or inhibiting the kit activation pathway by blocking binding of molecules in the downstream **signaling** pathway. The compound is preferably an antibody or portion thereof, preferably a monoclonal

antibody which is a human, humanized or chimeric antibody. The monoclonal antibody is preferably an anti-kit antibody, especially ACK2. The compound may comprise a Fab fragment of an anti-kit antibody or the variable domain of an anti-kit antibody. The compound may comprise one or more CDR portions of an anti-kit antibody. The antibody is preferably selected from immunoglobulin (Ig)A, IgD, IgE, IgG and IgM. The compound may also be a peptide, peptidomimetic, a nucleic acid or an organic compound with a molecular weight less than 500 Daltons. The compounds may be sSCF, SKIT ligand or a fragment of them. In the method for identifying a compound, composition or procedure which can reduce radiation damage, the radiation damage may be due to ultraviolet light, tanning, carcinogenesis, photo-aging, photo damage or development of melanoma. The epidermal **stem cell factor** transgene encodes either a membrane bound epidermal **stem cell factor** or a membrane/soluble epidermal **stem cell factor**. In the method for reducing skin response the skin response can be induced by applying an irritant or an allergic dermatitis inducing agent to the skin e.g. croton oil or dinitrofluorobenzene. In the method for testing for skin response compounds which may be tested include cosmetics, medications and skin care products.

ABEX

UPTX: 20001223

ADMINISTRATION - Administration is intralesional, intraperitoneal, intramuscular, subcutaneous, intravenous, by liposome mediate delivery, transmucosal, intestinal, topical, nasal, oral, anal, ocular, otic, intravesicular or parenteral. No dosage is specified.

=> => fil dpci

FILE 'DPCI' ENTERED AT 17:15:35 ON 12 AUG 2004

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FILE LAST UPDATED: 9 AUG 2004 <20040809/UP>

PATENTS CITATION INDEX, COVERS 1973 TO DATE

>>> LEARNING FILE LDPCI AVAILABLE <<<

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L94 ANSWER 1 OF 2 DPCI COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-483040 [52] DPCI

DNC C2001-144762

TI Treatment of mastocytosis involves administering indolinone derivatives or its salt to the patient.

DC B02

IN LONGLEY, B J

PA (UYCO) UNIV COLUMBIA NEW YORK

CYC 94

PI WO 2001047517 A1 20010705 (200152)* EN 44p A61K031-40

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
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LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001026083 A 20010709 (200164) A61K031-40

US 6339100 B1 20020115 (200208) A61K031-40

ADT WO 2001047517 A1 WO 2000-US35597 20001229; AU 2001026083 A AU 2001-26083
20001229; US 6339100 B1 US 1999-474474 19991229

FDT AU 2001026083 A Based on WO 2001047517

PRAI US 1999-474474 19991229

IC ICM A61K031-40

ICS A61K031-495

FS CPI

EXF EXAMINER'S FIELD OF SEARCH UPE: 20020731

NCL US 6339100 B1 20020115
 000/514.255; 000/514.412

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	4	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	2	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	2	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	1	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	35	Cited Literature References Count (by examiner)

CDP CITED PATENTS UPD: 20030709

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
US 6339100	B1	US 5883116	A 1999-214132/18
	PA:	(SUGE-N) SUGEN INC	
	IN:	MCMAHON, G; SUN, L; TANG, P C	
		US 5905149	A 1998-042101/04
	PA:	(PHAA) PHARMACIA & UPJOHN SPA	
	IN:	BALLINARI, D; BATTISTINI, C; BUZZETTI, F; ERMOLI, A; VIOGLIO, S	
		WO 9910325	A1 1999-190570/16
	PA:	(GLAX) GLAXO GROUP LTD; (GLAX) GLAXO WELLCOME INC	
	IN:	DICKERSON, S; HARRIS, P A; HUNTER, R N; JUNG, D K; LACKEY, K E; MCNUTT, R W; PEEL, M R; VEAL, J M; DICKERSON, S H	
		WO 9961422	A1 2000-086692/07
	PA:	(SUGE-N) SUGEN INC	
	IN:	MCMAHON, G; SUN, L; TANG, P C	
WO 200147517	A A	US 5883116	A 1999-214132/18
	PA:	(SUGE-N) SUGEN INC	
	IN:	MCMAHON, G; SUN, L; TANG, P C	
	A	US 5905149	A 1998-042101/04
	PA:	(PHAA) PHARMACIA & UPJOHN SPA	
	IN:	BALLINARI, D; BATTISTINI, C; BUZZETTI, F; ERMOLI, A; VIOGLIO, S	
	A	WO 9910325	A1 1999-190570/16
	PA:	(GLAX) GLAXO GROUP LTD; (GLAX) GLAXO WELLCOME INC	
	IN:	DICKERSON, S; HARRIS, P A; HUNTER, R N; JUNG, D K; LACKEY, K E; MCNUTT, R W; PEEL, M R; VEAL, J M; DICKERSON, S H	
	A	WO 9961422	A1 2000-086692/07
	PA:	(SUGE-N) SUGEN INC	
	IN:	MCMAHON, G; SUN, L; TANG, P C	

REN LITERATURE CITATIONS UPR: 20020731

 Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
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US 6339100	B1	Bradl, M., et al. (1991) "Clonal coat color variation due to a transforming gene expressed in melanocytes of transgenic mice" Proc. Nat. Acad. Sci. USA 88:6447-6451; (Exhibit 2).
US 6339100	B1	Costa, J. J. et al. (1996) "Recombinant human stem cell factor (KIT ligand) promotes human mast cell and melanocyte hyperplasia and functional activation in vivo" J. Exp. Med 183: 2681-2686; (Exhibit 3).
US 6339100	B1	Funasaka, Y., et al. (1992) "C-kit-kinase induces a cascade of protein tyrosine phosphorylation in normal human melanocytes in response to mast cell growth factor and stimulates mitogen-activated protein kinase but is down-regulated in melanomas" Mol. Biol. Cell, 3:197-209; (Exhibit 4).
US 6339100	B1	Furitsu, T., et al. (1993) Identification of mutations in the coding sequence of the proto-oncogene c-kit in human mast cell leukemia cell line causing ligand independent activation of c-KIT product J. Clin. Invest., 92:1736-1744; (Exhibit 5).
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US 6339100	B1	Longley, B. J. et al. (1995) "The mast cell and mast cell disease" J. Am. Acad. Dermatol., 32:545-561; (Exhibit 11).
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cell-conditioned medium" J. Biol. Chem., 266:8102-8107; (Exhibit 13).

US 6339100 B1 Nishikawa, S., et al. (1991) "In utero manipulation of coat color formation by a monoclonal anti-c-kit antibody: two distinct waves of c-kit-dependency during melanocyte development" EMBO J. 10:2111-2118; (Exhibit 14).

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- US 6339100 B1 Sun L, Tran N, Tang F, App H, Hirth P, McMahon G, Tang C: Synthesis and biological evaluations of 3-substituted indolin-2-ones: a novel class of tyrosine kinase inhibitors that exhibit selectivity toward particular receptor tyrosine kinases. J Med Chem 41: 2588-2603, 1998 (Exhibit 31).
- US 6339100 B1 Tsujimura T, Furitsu T, Morimoto M, Koji K, Nomura S, et al: Ligand-independent activation of c-kit receptor tyrosine kinase in a murine mastocytoma cell line P-815 generated by a point mutation. Blood 83: 2619-2626, 1994 (Exhibit 32).
- US 6339100 B1 Schrader, John W. and Thomas, Wayne R. "Delayed Hypersensitivity in Mast-Cell-Deficient Mice", The Journal of Immunology. (1983), vol. 130, No. 6, pp. 2565-2567 (Exhibit 33).
- US 6339100 B1 Galli, Stephen J. and Mekori, Yoseph A., "Undiminished Immunologic Tolerance to Contact Sensitivity in Mast Cell-Deficient W/Wv and S1/S1d Micel", The Journal of Immunology. (1995), vol. 135, No. 2, pp. 879-885 (Exhibit 34).
- US 6339100 B1 Askenase, Philip W., Loveren, Henk Van, Kraeuter-Kops, Sandra, Ron, Yacov, Meade, Robin, Theoharides, Theoharis C., Nordlund, James J., Scovern, Henry, Gerhson, Michael D., and Ptak, Wlodzimierz., "Defective Elicitation of Delayed-Type Hypersensitivity in W/Wv and SI/SId Mast Cell-Deficient Micel", The Journal of Immunology. (1983), vol. 131, No. 6, pp. 2687-2693 (Exhibit 35).

CGP CITING PATENTS

UPG: 20040108

Cited by Examiner

CITED PATENT	CAT	CITING PATENT	ACCNO
WO 200147517	A1 XP	WO 2003002105 A	2003-201461/12
	PA:	(ABSC-N) AB SCI	
	IN:	KINET, J; MOUSSY, A	
	XP	WO 2003002114 A	2003-312615/32
	PA:	(ABSC-N) AB SCI	
	IN:	KINET, J; MOUSSY, A	

L94 ANSWER 2 OF 2 DPCI COPYRIGHT 2004 THOMSON DERWENT on STN
 AN 2000-687622 [67] DPCI
 DNC C2000-209364

TI Prevention and treatment of contact dermatitis, hyperpigmentation, cutaneous inflammation and other conditions, comprises inhibiting the stem cell factor signaling pathway.

DC B04 D16 D21

IN **LONGLEY, B J**

PA (UYCO) UNIV COLUMBIA NEW YORK; (LONG-I) LONGLEY B J

CYC 90

PI WO 2000067794 A1 20001116 (200067)* EN 72p A61K039-395

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL
TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000048253 A 20001121 (200112) A61K039-395

US 2002123031 A1 20020905 (200260) C12Q001-00

US 6576812 B1 20030610 (200340) G01N033-00

ADT WO 2000067794 A1 WO 2000-US12405 20000505; AU 2000048253 A AU 2000-48253
20000505; US 2002123031 A1 CIP of US 1999-306143 19990506, US 1999-474478
19991229; US 6576812 B1 US 1999-306143 19990506

FDT AU 2000048253 A Based on WO 2000067794

PRAI US 1999-474478 19991229; US 1999-306143 19990506

IC ICM A61K039-395; C12Q001-00; G01N033-00

ICS A01K067-00; A01K067-027; A01K067-033; C07K016-00; C12Q001-70

FS CPI

EXF EXAMINER'S FIELD OF SEARCH UPE: 20030929

NCL US 6576812 B1 20030610
000/800.130; 000/800.140; 000/800.180; 000/800.300

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	3	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	1	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	1	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	1	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	27	Cited Literature References Count (by examiner)

CDP CITED PATENTS UPD: 20030929

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
US 6576812	B1	US 5877396	A 1995-382849/49
	PA:	(SLOK) SLOAN KETTERING INST CANCER RES	
	IN:	CLYNES, R; ONO, M; RAVETCH, J V; SYLVESTRE, D; TAKAI, T	
		US 5911988	A 1999-357170/30
	PA:	(FARB) BAYER CORP; (UNMI) UNIV MICHIGAN	
	IN:	BROWNELL, E; KUNKEL, S L; LUKACS, N; STRIETER, R M	

US 5997865 A 1995-358636/46
 PA: (GETH) GENENTECH INC; (BENN-I) BENNETT B D; (BROZ-I) BROZ S D; (MATT-I) MATTHEWS W; (ZEIG-I) ZEIGLER F C
 IN: BENNETT, B D; BROZ, S D; MATTHEWS, W; ZEIGLER, F C

WO 200067794 A A US 5877396 A 1995-382849/49
 PA: (SLOK) SLOAN KETTERING INST CANCER RES;
 IN: CLYNES, R; ONO, M; RAVETCH, J V; SYLVESTRE, D; TAKAI, T

US 5911988 A 1999-357170/30
 PA: (FARB) BAYER CORP; (UNMI) UNIV MICHIGAN
 IN: BROWNELL, E; KUNKEL, S L; LUKACS, N; STRIETER, R M

US 5997865 A 1995-358636/46
 PA: (GETH) GENENTECH INC; (BENN-I) BENNETT B D; (BROZ-I) BROZ S D; (MATT-I) MATTHEWS W; (ZEIG-I) ZEIGLER F C
 IN: BENNETT, B D; BROZ, S D; MATTHEWS, W; ZEIGLER, F C

REN LITERATURE CITATIONS UPR: 20030929

Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
US 6576812	B1	CA Kappel et al., Current Opinion in Biotechnology, "Regulating gene expression in transgenic animals," 1992, 3:548-553.*
US 6576812	B1	L-M Houdebine, Journal of Biotechnology, "Production of pharmaceutical proteins from transgenic animals," 1994, 34:269-287.*
US 6576812	B1	CD Sigmund, Arterioscler Thromb Vasc Biol., "Viewpoint: Are Studies in Genetically Altered Mice Out of Control?" 2000, 20:1425-1429.*
US 6576812	B1	RJ Wall, Theriogenology, "Transgenic Livestock: Progress and Prospects for the Future," 1996, 45:57-68.*
US 6576812	B1	Anderson, D.M., et al. (1990) "Molecular cloning of mast cell growth factor, a hematopoietin that is active in both membrane bound and soluble forms" Cell, 63:235-243 (Exhibit 2).
US 6576812	B1	Bradl, M., et al. (1991) "Clonal coat color variation due to a transforming gene expressed in melanocytes of transgenic mice" Proc. Nat. Acad. Sci. USA 88:6447-6451 (Exhibit 3).
US 6576812	B1	Costa, J. J. et al. (1996) "Recombinant human stem cell factor (KIT ligand) promotes human mast cell and melanocyte hyperplasia and functional activation in vivo" J. Exp. Med 183:2681-2686 (Exhibit 4).
US 6576812	B1	Funasaka, Y., et al. (1992) "C-kit-kinase induces a cascade of protein tyrosine phosphorylation in normal human melanocytes in response to mast cell growth factor and stimulates mitogen-activated protein kinase but is down-regulated in melanomas" Mol. Biol. Cell, 3:197-209 (Exhibit 5).
US 6576812	B1	Furitsu, T., et al. (1993) "Identification of mutations in the coding sequence of the proto-oncogene c-kit in human mast cell leukemia cell line causing ligand independent activation of c-KIT product" J. Clin. Invest., 92:1736-1744

(Exhibit 6).

US 6576812 B1 Grichnik, J. M., et al. (1995) "Human recombinant stem-cell factor induces melanocytic hyperplasia in susceptible patients" *J. Am. Acad. Dermatol.*, 33: 577-583 (Exhibit 7).

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US 6576812 B1 Harrist, T.J., et al. (1995) Recombinant human stem cell factor in (SCF) (c-kit ligand promotes melanocytes hyperplasia and activation in vivo *Lab. Invest.*, 72:48A (Exhibit 9).

US 6576812 B1 Hirobe, T. (1984) "Histochemical survey of the distribution of the epidermal melanoblasts and melanocytes in the mouse during fetal and postnatal periods" *Anat. Rec.*, 208:589-594 (Exhibit 10).

US 6576812 B1 Longley, B. J. et al. (1993) "Altered metabolism of mast-cell growth factor (c-kit ligand) in cutaneous mastocytosis" *N. Engl. J. Med.* . 328:1302-1307 (Exhibit 11).

US 6576812 B1 Longley, B. J. et al. (1995) "The mast cell and mast cell disease" *J. Am. Acad. Dermatol.*, 32:545-561 (Exhibit 12).

US 6576812 B1 Longley, B. J., et al. (1996) "Somastic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm" *Nature Genetics*, 12:312-314 (Exhibit 13).

US 6576812 B1 Lu, H. S., et al. (1991) "Amino acid sequence and post-translational modification of stem cell factor isolated from buffalo rat liver cell-conditioned medium" *J. Biol. Chem.*, 266:8102-8107 (Exhibit 14).

US 6576812 B1 Nishikawa, S., et al. (1991) "In utero manipulation of coat color formation by a monoclonal anti-c-kit antibody: two distinct waves of c-kit-dependency during melanocyte development" *EMBO J.* 10:2111-2118 (Exhibit 15).

US 6576812 B1 Okura, M., et al. (1995) "Effects of monoclonal anti-c-kit antibody (AKC2) on melanocytes in newborn mice" *J. Invest. Dermatol.*, 105:322-328 (Exhibit 16).

US 6576812 B1 Tsai, M., et al. (1991) "The rat c-kit ligand, stem cell factor, induces the development of connective tissue-type and mucosal mast cells in vivo: analysis by anatomical distribution, histochemistry, and protease phenotype" *J. Exp. Med.*, 174:125-131 (Exhibit 17).

US 6576812 B1 Vassar, R., et al. (1989) "Tissue-specific and differentiation-specific expression of a human K14 keratin gene in transgenic mice" *Proc. Natl. Acad. Sci. USA*, 86:1563-1567 (Exhibit 18).

US 6576812 B1 Weiss, R. R. et al. (1995) "Human dermal endothelial cells express membrane-associated mast cell growth factor" *J. Invest. Dermatol.* 104:101-106 (Exhibit 19).

US 6576812 B1 Williams, D.E., et al. (1990) "Identification of a ligand for the c-kit proto-oncogene" *Cell*, 1990;63:167-174 (Exhibit 20).

US 6576812 B1 Yarden, Y., et al. (1987) "Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand" *EMBO J.* 6:3341-3351

(Exhibit 21).
 US 6576812 B1 Yoshida, H., et al. (1996) "Distinct stages of melanocyte differentiation revealed by analysis of nonuniform pigmentation patterns" Development, 122:1207-1214 (Exhibit 22).
 US 6576812 B1 Yoshida, H. et al. (1996) "Neural and skin cell-specific expression pattern conferred by Steel factor regulatory sequence in transgenic mice" Development Dynamic, 207:222-232 (Exhibit 23).
 US 6576812 B1 Zsebo, K. M., et al. (1990) "Stem cell factor is encoded at the S1 locus of the mouse and is the ligand for the c-kit tyrosine kinase receptor" Cell, 63:213-224 (Exhibit 24).

CGP CITING PATENTS

UPG: 20040505

Cited by Examiner

CITED PATENT	CAT	CITING PATENT	ACCNO
WO 200067794	A X	WO 2003024386	A 2003-371772/32
	PA:	(ABSC-N) AB SCI	
	IN:	KINET, J; MOUSSY, A	

=> => fil medline

FILE 'MEDLINE' ENTERED AT 17:26:21 ON 12 AUG 2004

FILE LAST UPDATED: 12 AUG 2004 (20040812/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot

L114 ANSWER 1 OF 2 MEDLINE on STN

AN 1999002668 MEDLINE

DN PubMed ID: 9788619

TI Lck associates with and is activated by Kit in a small cell lung cancer cell line: **inhibition** of SCF-mediated growth by the Src family kinase **inhibitor** PP1.

AU Krystal G W; DeBerry C S; Linnekin D; Litz J

CS Department of Medicine, Medical College of Virginia Commonwealth University, McGuire Veterans Affairs Medical Center, Richmond 23249, USA.. GKRYSTAL@GEMS.VCU.edu

SO Cancer research, (1998 Oct 15) 58 (20) 4660-6.

Journal code: 2984705R. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199811

ED Entered STN: 19990106
Last Updated on STN: 20000303
Entered Medline: 19981106

AB At least 70% of small cell lung cancers (SCLCs) express the Kit receptor tyrosine kinase and its ligand, stem cell factor (SCF). In an effort to define the **signal** transduction **pathways** activated by Kit in SCLC, we focused on Src family kinases and, in particular, Lck, a Src-related tyrosine kinase that is expressed in hemopoietic cells and certain tumors, including SCLC. SCF treatment of the H526 cell line induced a physical association between Kit and Lck that, in vitro, was dependent on phosphorylation of the juxtamembrane domain of Kit. Stimulation of Kit with recombinant SCF resulted in a rapid 3-6-fold increase in the specific activity of Lck, which was similar in magnitude to the activation of Lck resulting from the cross-linking of the T-cell receptor complex of Jurkat cells. Lck activity peaked by 5 min after SCF addition, and the elevated activity persisted for at least 30 min in the presence of SCF, with kinetics similar to the activation of mitogen-activated protein kinase. PP1, an **inhibitor** of Src family kinases with selectivity for Lck, completely **inhibited** SCF-mediated growth but had little effect on insulin-like growth factor-I-mediated growth. PP1 antagonized both SCF-mediated proliferation and **inhibition** of apoptosis. PP1 had no effect on Kit kinase activity but was shown to block total Lck activity by at least 90% by immune complex kinase assay. Low levels of Src, Hck, and Yes were also expressed in the H526 cell line; only Yes showed a consistent increase in specific activity, which was also **inhibited** by PP1 following SCF treatment. These data demonstrate that, in the H526 SCLC cell line, Lck and, possibly, Yes are downstream of Kit in a **signal** transduction **pathway**; the **inhibition** by PP1 of SCF-mediated proliferation and **inhibition** of apoptosis suggests that Src family kinases are intermediates in the **signaling pathways** that regulate these processes.

CT Check Tags: Human; Support, U.S. Gov't, Non-P.H.S.
*Carcinoma, Small Cell: DT, drug therapy
Carcinoma, Small Cell: ME, metabolism
*Enzyme Inhibitors: PD, pharmacology
Jurkat Cells
*Lung Neoplasms: DT, drug therapy
Lung Neoplasms: ME, metabolism
*Lymphocyte Specific Protein Tyrosine Kinase p56(lck): PH, physiology
*Proto-Oncogene Protein c-kit: PH, physiology
Pyrazoles: PD, pharmacology
Pyrimidines: PD, pharmacology
Signal Transduction
*Stem Cell Factor: AI, antagonists & inhibitors
Stem Cell Factor: PD, pharmacology
*src-Family Kinases: AI, antagonists & inhibitors

CN 0 (4-amino-5-(4-methylphenyl)-7-(tert-butyl)pyrazolo(3,4-d)pyrimidine); 0 (Enzyme Inhibitors); 0 (Pyrazoles); 0 (Pyrimidines); 0 (Stem Cell Factor); EC 2.7.1.112 (Proto-Oncogene Protein c-kit); EC 2.7.1.112 (src-Family Kinases); EC 2.7.1.37 (Lymphocyte Specific Protein Tyrosine Kinase p56(lck))

L114 ANSWER 2 OF 2 MEDLINE on STN
AN 97304300 MEDLINE
DN PubMed ID: 9160663
TI Macrophage inflammatory protein-1alpha and interferon-inducible protein 10 **inhibit** synergistically induced growth factor stimulation of MAP kinase activity and suppress phosphorylation of eukaryotic initiation factor 4E and 4E binding protein 1.

AU Aronica S M; Gingras A C; Sonenberg N; Cooper S; Hague N; Broxmeyer H E
CS Department of Microbiology/Immunology, Walther Oncology Center, Indiana University School of Medicine, Indianapolis 46202-5121, USA.

SO Blood, (1997 May 15) 89 (10) 3582-95.
 Journal code: 7603509. ISSN: 0006-4971.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199706

ED Entered STN: 19970630
 Last Updated on STN: 19980206
 Entered Medline: 19970619

AB Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Steel factor (SLF) synergistically stimulate Raf-1 kinase activity, protein synthesis, and proliferation in hematopoietic MO7e cells; synergistic action of these factors is blocked by the suppressive chemokines macrophage inflammatory protein-1alpha (MIP-1alpha) and interferon-inducible protein 10 (IP-10; Aronica et al, J Biol Chem 270:21998, 1995). We assessed the potential for both stimulatory and inhibitory factors to act through the MAP kinase **signaling pathway** by studying the effects of growth factors and chemokines on MAP kinase activation. Also, because activation of kinase **signaling pathways** and stimulation of protein synthesis by peptide growth factors are associated with increased phosphorylation of eukaryotic initiation factor 4E (eIF-4E) and the translational repressor 4E-binding protein 1 (4E-BP1) in some target cells, we investigated whether growth factor treatment could alter eIF-4E or 4E-BP1 phosphorylation state in MO7e cells. We report that treatment of MO7e cells with GM-CSF and SLF stimulated significant, greater-than-additive increases in MAP kinase activity and the phosphorylation of both eIF-4E and 4E-BP1. Increased 4E-BP1 phosphorylation correlated with a decrease in the association of 4E-BP1 with eIF-4E. Growth factor-induced phosphorylation of 4E-BP1 and dissociation of 4E-BP1 from eIF-4E was blocked in cells treated with rapamycin, wortmannin, or PD098059. Treatment of cells with IP-10 or MIP-1alpha blocked the stimulatory effects of GM-CSF and SLF, resulting in suppression of MAP kinase activity, eIF-4E and 4E-BP1 phosphorylation, and eIF-4E/4E-BP1 dissociation. Our results suggest that GM-CSF and SLF exert part of their combined growth-promoting effects on MO7e cells through activation of MAP kinase and enhancement of eIF-4E and 4E-BP1 phosphorylation and dissociation and that suppression of growth factor-induced protein synthesis by MIP-1alpha and IP-10 involves translational repression at the level of eIF-4E.

CT Check Tags: Human
 8-Bromo Cyclic Adenosine Monophosphate: PD, pharmacology
 *Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
 *Carrier Proteins
 *Chemokines, CXC
 Cyclic AMP: PD, pharmacology
 *Cytokines: PD, pharmacology
 Drug Synergism
 Enzyme Activation: DE, drug effects
 Eukaryotic Initiation Factor-4E
 Forskolin: PD, pharmacology
 *Granulocyte-Macrophage Colony-Stimulating Factor: AI, antagonists & inhibitors
 Granulocyte-Macrophage Colony-Stimulating Factor: PD, pharmacology
 *Growth Inhibitors: PD, pharmacology
 Leukemia, Megakaryocytic, Acute: PA, pathology
 *Macrophage Inflammatory Protein-1: PD, pharmacology
 Neoplasm Proteins: ME, metabolism
 *Peptide Initiation Factors: ME, metabolism
 *Phosphoproteins: ME, metabolism
 Phosphorylation: DE, drug effects
 *Protein Processing, Post-Translational: DE, drug effects
 Recombinant Proteins: AI, antagonists & inhibitors

Recombinant Proteins: PD, pharmacology
Signal Transduction: DE, drug effects
*Stem Cell Factor: AI, antagonists & inhibitors
Stem Cell Factor: PD, pharmacology

Tumor Cells, Cultured: DE, drug effects

RN 23583-48-4 (8-Bromo Cyclic Adenosine Monophosphate); 60-92-4 (Cyclic AMP);
66428-89-5 (Forskolin); 83869-56-1 (Granulocyte-Macrophage
Colony-Stimulating Factor)
CN 0 (CXC chemokine IP-10); 0 (Carrier Proteins); 0 (Chemokines, CXC); 0
(Cytokines); 0 (Eukaryotic Initiation Factor-4E); 0 (Growth
Inhibitors); 0 (Macrophage Inflammatory Protein-1); 0 (Neoplasm
Proteins); 0 (PHAS-I protein); 0 (Peptide Initiation Factors); 0
(Phosphoproteins); 0 (Recombinant Proteins); 0 (Stem Cell Factor); EC
2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase)

=> => fil biosis

FILE 'BIOSIS' ENTERED AT 17:28:38 ON 12 AUG 2004

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FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 11 August 2004 (20040811/ED)

FILE RELOADED: 19 October 2003.

=> d l119 all tot

L119 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 1999:357104 BIOSIS

DN PREV199900357104

TI SCF-KIT pathway in human epidermal melanocyte homeostasis (and
reply).

AU Longley, B. Jack [Reprint author]; Carter, Eric L.; Grichnik,
James M.

CS Section of Dermopathology, College of Physicians and Surgeons, Columbia
University, 630 West 168 Street, VC 5-578, New York, NY, 10032, USA

SO Journal of Investigative Dermatology, (July, 1999) Vol. 113, No. 1, pp.
139-140. print.

CODEN: JIDEAE. ISSN: 0022-202X.

DT Letter

LA English

ED Entered STN: 2 Sep 1999

Last Updated on STN: 2 Sep 1999

CC Integumentary system - General and methods 18501

Cytology - Animal 02506

Cytology - Human 02508

Biochemistry studies - General 10060

Metabolism - General metabolism and metabolic pathways 13002

Endocrine - General 17002

IT Major Concepts

Chemical Coordination and Homeostasis; Integumentary System (Chemical
Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms

epidermis: integumentary system; melanocytes: integumentary system,
homeostasis

IT Chemicals & Biochemicals

stem cell factor; KIT: activation

ORGN Classifier

Hominidae 86215

Super Taxa

Primates; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

human

Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier

Muridae 86375

Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

mouse: animal model

Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

L119 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 1999:263271 BIOSIS

DN PREV199900263271

TI Inhibition of spontaneous receptor phosphorylation by residues in a putative alpha-helix in the KIT intracellular juxtamembrane region.

AU Ma, Yongsheng; Cunningham, Matthew E.; Wang, Xiaomei; Ghosh, Indraneel; Regan, Lynn; Longley, B. Jack [Reprint author]

CS Dept. of Dermatology, Section of Dermatopathology, College of Physicians and Surgeons, Columbia University, 630 West 168th St., Vanderbilt Clinic 15-221, New York, NY, 10032, USA

SO Journal of Biological Chemistry, (May 7, 1999) Vol. 274, No. 19, pp. 13399-13402. print.

CODEN: JBCHA3. ISSN: 0021-9258.

DT Article

LA English

ED Entered STN: 15 Jul 1999

Last Updated on STN: 15 Jul 1999

AB KIT receptor kinase activity is repressed, prior to stem

cell factor binding, by unknown structural constraints.

Using site-directed mutagenesis, we examined the role of KIT intracellular juxtamembrane residues Met-552 through Ile-563 in controlling receptor auto-phosphorylation. Alanine substitution for Tyr-553, Trp-557, Val-559, or Val-560, all sitting along the hydrophobic side of an amphipathic alpha-helix (Tyr-553-Ile-563) predicted by the Chou-Fasman algorithm, resulted in substantially increased spontaneous receptor phosphorylation, revealing inhibitory roles for these residues. Alanine substitution for other residues, most of which are on the hydrophilic side of the helix, caused no or slightly increased basal receptor phosphorylation.

Converting Tyr-553 or Trp-557 to phenylalanine generated slight or no elevation, respectively, in basal KIT phosphorylation, indicating that the phenyl ring of Tyr-553 and the hydrophobicity of Trp-557 are critical for the inhibition. Although alanine substitution for Lys-558 had no effect on receptor phosphorylation, its substitution with proline produced high spontaneous receptor phosphorylation, suggesting that the predicted alpha-helical conformation is involved in the inhibition. A synthetic peptide comprising Tyr-553 through Ile-563 showed circular dichroism spectra characteristic of alpha-helix, supporting the structural prediction. Thus, the KIT intracellular juxtamembrane region contains important residues which, in a putative alpha-helical conformation, exert inhibitory control on the kinase activity of ligand-unoccupied receptor.

CC Enzymes - Chemical and physical 10806

Biochemistry methods - Proteins, peptides and amino acids 10054

Biophysics - Methods and techniques 10504

Biophysics - Molecular properties and macromolecules 10506

General biology - Miscellaneous 00532

IT Major Concepts

Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques

IT Chemicals & Biochemicals
KIT receptor kinase: intracellular juxtamembrane region

IT Methods & Equipment
circular dichroism: analytical method, spectroscopic techniques: CB, spectroscopic techniques: CT; immunoblotting: Analysis/Characterization Techniques: CB, analytical method; immunoprecipitation: isolation method, precipitation techniques; site-directed mutagenesis: analytical method, mutagenesis, protein engineering; transfection: gene expression/vector techniques, genetic method

IT Miscellaneous Descriptors
amino acid substitution; spontaneous receptor phosphorylation: inhibition

ORGN Classifier
Cercopithecidae 86205
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
COS cell line
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Mammals, Nonhuman Vertebrates, Nonhuman Primates, Primates, Vertebrates

RN 9031-44-1 (KINASE)

L119 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1999:229797 BIOSIS
DN PREV199900229797
TI Transgenic mice expressing **stem cell factor**
in basal keratinocytes develop postinflammatory hyperpigmentation in response to irritant and allergic contactants.
AU Carter, E. L. [Reprint author]; Tigelaar, R. E.; Longley, B. J.
CS Department of Dermatology, Columbia University, New York, NY, USA
SO Journal of Investigative Dermatology, (April, 1999) Vol. 112, No. 4, pp. 539. print.
Meeting Info.: 60th Annual Meeting of the Society for Investigative Dermatology. Chicago, Illinois, USA. May 5-9, 1999.
CODEN: JIDEAE. ISSN: 0022-202X.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English
ED Entered STN: 17 Jun 1999
Last Updated on STN: 17 Jun 1999

CC Integumentary system - General and methods 18501
Cytology - Animal 02506
Biochemistry studies - General 10060
Blood - General and methods 15001
Immunology - General and methods 34502
Allergy 35500
Toxicology - General and methods 22501
Endocrine - General 17002
General biology - Symposia, transactions and proceedings 00520

IT Major Concepts
Allergy (Clinical Immunology, Human Medicine, Medical Sciences);
Dermatology (Human Medicine, Medical Sciences)

IT Parts, Structures, & Systems of Organisms
basal keratinocyte: integumentary system; epidermis: integumentary system

IT Diseases
postinflammatory hyperpigmentation: integumentary system disease

IT Chemicals & Biochemicals
allergic contactant: allergen; irritant contactant: toxin; keratin 14 promoter; **stem cell factor**: expression

IT Miscellaneous Descriptors
Meeting Abstract

ORGN Classifier

Muridae 86375

Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

mouse: model, transgenic

Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
Rodents, Vertebrates

L119 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 1998:304050 BIOSIS

DN PREV199800304050

TI Murine cutaneous mastocytosis and epidermal melanocytosis induced by
keratinocyte expression of transgenic **stem cell factor**.AU Kunisada, Takahiro [Reprint author]; Lu, Shu-Zhuang; Yoshida, Hisahiro;
Nishikawa, Satomi; Nishikawa, Shin-Ichi; Mizoguchi, Masako; Hayashi,
Shin-Ichi; Tyrrell, Lynda; Williams, David A.; Wang, Xiaomei;
Longley, B. Jack [Reprint author]CS Sect. Dermatopathol., Coll. Physicians Surg. Columbia Univ., 630 W. 168th
St., VC 5-578, New York, NY 10032, USASO Journal of Experimental Medicine, (May 18, 1998) Vol. 187, No. 10, pp.
1565-1573. print.

CODEN: JEMEAV. ISSN: 0022-1007.

DT Article

LA English

ED Entered STN: 15 Jul 1998

Last Updated on STN: 15 Jul 1998

AB The growth and differentiation of mast cells and melanocytes require
stem cell factor (SCF), the ligand

for the kit receptor tyrosine kinase. **SCF** may exist as a membrane-bound or soluble molecule. Abnormalities of the **SCF**-kit signaling pathway, with increased local concentrations of soluble **SCF**, have been implicated in the pathogenesis of the human disease cutaneous mastocytosis, but have not yet been shown to play a causal role. To investigate both the potential of **SCF** to cause mastocytosis and its role in epidermal melanocyte homeostasis, we targeted the expression of **SCF** to epidermal keratinocytes in mice with two different transgenes controlled by the human keratin 14 promoter. The transgenes contained cDNAs that either produced **SCF**, which can exist in both membrane-bound and soluble forms, or **SCF**, which remains essentially membrane bound. Murine epidermal keratinocyte expression of membrane-bound/ soluble **SCF** reproduced the phenotype of human cutaneous mastocytosis, with dermal mast cell infiltrates and epidermal hyperpigmentation, and caused the maintenance of a population of melanocytes in the interadnexal epidermis, an area where melanocytes and melanin are found in human skin but where they are not typically found in murine skin. Expression of membrane-bound **SCF** alone resulted in epidermal melanocytosis and melanin production, but did not by itself cause mastocytosis. We conclude, first, that a phenotype matching that of human mastocytosis can be produced in mice by keratinocyte overproduction of soluble **SCF**, suggesting a potential cause of this disease. Second, we conclude that keratinocyte expression of membrane-bound **SCF** results in the postnatal maintenance of epidermal melanocytes in mice. Since the resulting animals have skin that more closely approximates human skin than do normal mice, their study may be more relevant to human melanocyte biology than the study of skin of normal mice.

CC Integumentary system - General and methods 18501

Genetics - Animal 03506

Biochemistry studies - General 10060

IT Major Concepts

Integumentary System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms
interadnexal epidermis: integumentary system; keratinocyte:
integumentary system; mast cell: immune system

IT Diseases
cutaneous mastocytosis: congenital disease, integumentary system
disease
Mastocytosis (MeSH)

IT Diseases
epidermal melanocytosis: integumentary system disease

IT Chemicals & Biochemicals
melanin; transgenic **stem cell factor**:
expression

IT Miscellaneous Descriptors
melanocyte development

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: transgenic
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
Rodents, Vertebrates

L119 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:122069 BIOSIS
DN PREV199800122069
TI **SCF** and c-kit in mastocytosis. A Pandora's box holding more
theories than proven facts (and reply).
AU Henz, Beate M. [Reprint author]; **Longley, B. Jack**
CS Dep. Dermatol., Free Univ. Berlin, Rudolf Virchow Hosp., Berlin, Germany
SO Journal of Investigative Dermatology, (Feb., 1998) Vol. 110, No. 2, pp.
186-187. print.
CODEN: JIDEAE. ISSN: 0022-202X.

DT Letter
LA English
ED Entered STN: 5 Mar 1998
Last Updated on STN: 5 Mar 1998

CC Integumentary system - General and methods 18501
Endocrine - General 17002
Pediatrics - 25000
Development and Embryology - General and descriptive 25502

IT Major Concepts
Integumentary System (Chemical Coordination and Homeostasis)

IT Diseases
mastocytosis: congenital disease, integumentary system disease
Mastocytosis (MeSH)

IT Chemicals & Biochemicals
c-kit: mutation; stem cell growth factor

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human: child
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L119 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:434032 BIOSIS
DN PREV199799733235
TI Chymase cleavage of **stem cell factor** yields

a bioactive, soluble product.

AU Longley, B. Jack [Reprint author]; Tyrrell, Lynda; Ma, Yongsheng; Williams, David A.; Halaban, Ruth; Langley, Keith; Lu, Hsieng S.; Schechter, Norman M.

CS Sect. Dermatopathol., Coll. Physicians Surgeons Columbia Univ., 630 West 168th St., VC5-578, New York, NY 10032, USA

SO Proceedings of the National Academy of Sciences of the United States of America, (1997) Vol. 94, No. 17, pp. 9017-9021.
CODEN: PNASA6. ISSN: 0027-8424.

DT Article

LA English

ED Entered STN: 8 Oct 1997
Last Updated on STN: 8 Oct 1997

AB **Stem cell factor (SCF)** is produced by stromal cells as a membrane-bound molecule, which may be proteolytically cleaved at a site close to the membrane to produce a soluble bioactive form. The proteases producing this cleavage are unknown. In this study, we demonstrate that human mast cell chymase, a chymotrypsin-like protease, cleaves **SCF** at a novel site. Cleavage is at the peptide bond between Phe-158 and Met-159, which are encoded by exon 6 of the **SCF** gene. This cleavage results in a soluble bioactive product that is 7 amino acids shorter at the C terminus than previously identified soluble **SCF**. This research shows the identification of a physiologically relevant enzyme that specifically cleaves **SCF**. Because mast cells express the KIT protein, the receptor for **SCF**, and respond to **SCF** by proliferation and degranulation, this observation identifies a possible feedback loop in which chymase released from mast cell secretory granules may solubilize **SCF** bound to the membrane of surrounding stromal cells. The liberated soluble **SCF** may in turn stimulate mast cell proliferation and differentiated functions; this loop could contribute to abnormal accumulations of mast cells in the skin and hyperpigmentation at sites of chronic cutaneous inflammation.

CC Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - Physiological studies 10808

IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics)

IT Chemicals & Biochemicals
CHYMASE

IT Miscellaneous Descriptors
ACTIVITY; CHYMASE; CLEAVAGE; ENZYME SUBSTRATE; ENZYMOLOGY; MAST CELL ENZYME; MEMBRANE MOLECULE; SOLUBLE BIOACTIVE FORM; **STEM CELL FACTOR**; STOMAL CELL POLYPEPTIDE

RN 97501-92-3 (CHYMASE)

L119 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 1997:345950 BIOSIS

DN PREV199799645153

TI Human skin/SCID mouse chimeras an an in vivo model for human cutaneous mast cell hyperplasia.

AU Christofidou-Solomidou, Melpo; Longley, B. Jack; Whitaker-Menezes, Diana; Albelda, Steven M.; Murphy, George F. [Reprint author]

CS Jefferson Alumni Hall, Suite 545, 1020 Locust St., Philadelphia, PA 19107-6799, USA

SO Journal of Investigative Dermatology, (1997) Vol. 109, No. 1, pp. 102-107.
CODEN: JIDEAE. ISSN: 0022-202X.

DT Article

LA English

ED Entered STN: 11 Aug 1997
Last Updated on STN: 11 Aug 1997

AB Human skin xenografted to mice with severe combined immunodeficiency

syndrome (SCID) was evaluated to determine the integrity and fate of human dermal mast cells. There was an approximately 3-fold increase in number of dermal mast cells by 3 mo after engraftment ($p < 0.05$). These cells were responsive to conventional mast cell secretagogues and were confirmed to be of human origin by ultrastructural characterization of granule substructure and by reactivity for the human mast cell proteinase, chymase. CD1a+ Langerhans cells, also bone marrow-derived cells, failed to show evidence of concomitant hyperplasia, and increased mast cell number was not associated with alterations in number of dermal vascular profiles identified immunohistochemically for human CD31. RT-PCR analysis demonstrated human but not murine **stem cell factor** (SCF; also termed mast cell growth factor, c-kit ligand) mRNA in xenografts. Epidermal reactivity for **stem cell factor** protein shifted from a cytoplasmic pattern to an intercellular pattern by 3 mo after engraftment, suggesting a secretory phenotype, as previously documented for human cutaneous mastocytosis. The majority ($> 90\%$) of mast cells demonstrated membrane reactivity for human SCF at the time points of peak hyperplasia. These data establish SCID mouse recipients of human skin xenografts as a potential in vivo model for cutaneous mast cell hyperplasia.

CC Cytology - Animal 02506
Cytology - Human 02508
Anatomy and Histology - Regeneration and transplantation 11107
Blood - General and methods 15001
Endocrine - General 17002
Integumentary system - General and methods 18501

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology;
Endocrine System (Chemical Coordination and Homeostasis); Integumentary
System (Chemical Coordination and Homeostasis); Physiology

IT Miscellaneous Descriptors
CONGENITAL DISEASE; CUTANEOUS MAST CELL HYPERPLASIA; CUTANEOUS
MASTOCYTOSIS; DERMAL MAST CELL; HUMAN SKIN XENOGRAFT; IMMUNE SYSTEM;
INTEGUMENTARY SYSTEM; INTEGUMENTARY SYSTEM DISEASE; MESSENGER RNA;
MRNA; SCID MOUSE; SEVERE COMBINED IMMUNODEFICIENCY MOUSE; **STEM
CELL FACTOR**

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Muridae
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
Rodents, Vertebrates

=> s l116 not l119

L121 7 L116 NOT L119

=> d all tot

L121 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2004:255424 BIOSIS
DN PREV200400254772

TI Autoimmune cutaneous hypopigmentation following DNA vaccination with TRP-2
 in SCF transgenic mice: Mimicking vitiligo in humans.
 AU Trcka, J. [Reprint Author]; Engelhorn, M.; Schaed, S. G. [Reprint Author];
 Carter, E.; Broecker, E. B. [Reprint Author]; Longley, B. J.;
 Houghton, A. N.
 CS Univ.-Hautklinik, 97080, Wuerzburg, Germany
 SO Archives of Dermatological Research, (February 2004) Vol. 295, No. 8-9,
 pp. 382. print.
 Meeting Info.: 31st Annual Meeting of the Arbeitsgemeinschaft
 Dermatologische Forschung in cooperation with the Deutsche Dermatologische
 Gesellschaft. Berlin, Germany. February 26-28, 2004.
 ISSN: 0340-3696 (ISSN print).
 DT Conference; (Meeting)
 Conference; (Meeting Poster)
 Conference; Abstract; (Meeting Abstract)
 LA English
 ED Entered STN: 12 May 2004
 Last Updated on STN: 12 May 2004
 CC General biology - Symposia, transactions and proceedings 00520
 Cytology - Animal 02506
 Integumentary system - Physiology and biochemistry 18504
 Integumentary system - Pathology 18506
 Immunology - General and methods 34502
 Immunology - Immunopathology, tissue immunology 34508
 IT Major Concepts
 Immune System (Chemical Coordination and Homeostasis); Integumentary
 System (Chemical Coordination and Homeostasis)
 IT Parts, Structures, & Systems of Organisms
 epidermal keratinocyte: integumentary system; melanocyte: integumentary
 system; skin: integumentary system
 IT Diseases
 autoimmune cutaneous hypopigmentation: immune system disease;
 integumentary system disease
 IT Diseases
 vitiligo: integumentary system disease
 Vitiligo (MeSH)
 IT Chemicals & Biochemicals
 cytokeratin 14: promoter activity; tyrosinase related protein-2 [TRP-2]
 IT Methods & Equipment
 DNA vaccination: genetic techniques, laboratory techniques;
 immunization: clinical techniques, therapeutic and prophylactic
 techniques
 IT Miscellaneous Descriptors
 tumor immunity
 ORGN Classifier
 Muridae 86375
 Super Taxa
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 C57/BL6 mouse (common): transgenic
 Taxa Notes
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
 Rodents, Vertebrates
 GEN mouse SCF gene [mouse stem cell
 factor gene] (Muridae): transgene
 L121 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2004:188195 BIOSIS
 DN PREV200400184749
 TI A role for SCF/c-kit signaling in the morphogenesis and cyclic
 regeneration of hair pigmentation unit.
 AU Botchkareva, N. V. [Reprint Author]; Botchkarev, V. A. [Reprint Author];
 Khlgatian, M. [Reprint Author]; Sharov, A. A. [Reprint Author];

- Longley, B. J.; Gilchrest, B. A. [Reprint Author]**
 CS Dept. of Dermatology, Boston University School of Medicine, Boston, USA
 SO Journal of Investigative Dermatology Symposium Proceedings, (June 2003)
 Vol. 8, No. 1, pp. 128. print.
 Meeting Info.: Third Intercontinental Meeting of Hair Research Societies.
 Tokyo, Japan. June 13-15, 2001.
 ISSN: 1087-0024 (ISSN print).
- DT Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
- LA English
- ED Entered STN: 7 Apr 2004
 Last Updated on STN: 7 Apr 2004
- CC General biology - Symposia, transactions and proceedings 00520
 Cytology - Animal 02506
 Biochemistry studies - General 10060
 Enzymes - General and comparative studies: coenzymes 10802
 Integumentary system - Physiology and biochemistry 18504
- IT Major Concepts
 Biochemistry and Molecular Biophysics; Integumentary System (Chemical
 Coordination and Homeostasis)
- IT Parts, Structures, & Systems of Organisms
 hair: integumentary system; hair follicle: integumentary system;
 keratinocytes: integumentary system; melanocyte: integumentary system
- IT Chemicals & Biochemicals
 SCF/c-kit: signaling; c-kit; c-kit receptor; melanogenic
 proteins; tyrosinase [EC 1.14.18.1]
- IT Methods & Equipment
 double immunofluorescence: immunologic techniques, laboratory
 techniques; multi-color confocal microscopy: imaging and microscopy
 techniques, laboratory techniques
- IT Miscellaneous Descriptors
 morphogenesis
- RN 9002-10-2 (tyrosinase)
 9002-10-2 (EC 1.14.18.1)
- L121 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2003:435404 BIOSIS
 DN PREV200300435404
 TI Effects of tyrosine kinase inhibitor STI571 on human mast cells bearing
 wild-type or mutated c-kit.
 AU Akin, Cem [Reprint Author]; Brockow, Knut; D'Ambrosio, Claudio;
 Kirshenbaum, Arnold S.; Ma, Yongsheng; Longley, B. Jack;
 Metcalfe, Dean D.
 CS Laboratory of Allergic Diseases, NIAID/NIH, 10 Center Drive, Building 10,
 Room 11C205, MSC 1881, Bethesda, MD, 20892-1881, USA
 cakin@niaid.nih.gov
 SO Experimental Hematology (New York), (August 2003) Vol. 31, No. 8, pp.
 686-692. print.
 ISSN: 0301-472X (ISSN print).
- DT Article
- LA English
- ED Entered STN: 17 Sep 2003
 Last Updated on STN: 17 Sep 2003
- AB Objective: STI571 is a tyrosine kinase inhibitor which inhibits the kinase
 activity of kit, the receptor for **stem cell**
factor (SCF). Because activating mutations of c-kit
 affecting codon 816 are associated with human mast cell neoplasms, we
 determined whether STI571 exerted a similar cytotoxic effect on neoplastic
 and normal human mast cells. Methods: We investigated the effect of
 addition of STI571 in increasing concentrations (0.01 to 10 micromolar) to
 two HMC-1 human mast cell leukemia cell lines carrying two different
 activating c-kit mutations in codons 816 or 560, as well as the effect of
 the drug on short-term bone marrow cultures obtained from patients who

carry a mutated codon 816 or wild-type c-kit. Results: STI571 failed to inhibit the growth of HMC-1560,816 cells bearing a codon 816 mutation but effectively suppressed the proliferation of HMC-1560 carrying c-kit with the wild-type codon 816. STI571 did not induce preferential killing of neoplastic bone marrow mast cells in short-term cultures from patients bearing a codon 816 c-kit mutation. In contrast, STI571 caused a dramatic reduction in mast cells in patients without codon 816 c-kit mutations. Conclusion: These results suggest that STI571, while effectively killing mast cells with wild-type c-kit, did not show preferential cytotoxicity to neoplastic human mast cells and thus may not be effective in the treatment of human systemic mastocytosis associated with codon 816 c-kit mutations.

CC Cytology - Animal 02506
 Cytology - Human 02508
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Enzymes - General and comparative studies: coenzymes 10802
 Pathology - Therapy 12512
 Blood - Blood and lymph studies 15002
 Blood - Blood cell studies 15004
 Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
 Integumentary system - Pathology 18506
 Pharmacology - General 22002
 Pharmacology - Clinical pharmacology 22005
 Neoplasms - Immunology 24003
 Neoplasms - Pathology, clinical aspects and systemic effects 24004
 Neoplasms - Therapeutic agents and therapy 24008
 Neoplasms - Blood and reticuloendothelial neoplasms 24010
 Gerontology 24500
 Pediatrics 25000
 Development and Embryology - Pathology 25503
 Tissue culture, apparatus, methods and media 32500
 Immunology - General and methods 34502
 Immunology - Immunopathology, tissue immunology 34508

IT Major Concepts
 Clinical Immunology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences); Pharmacology

IT Parts, Structures, & Systems of Organisms
 bone marrow: blood and lymphatics, immune system; mast cells: immune system

IT Diseases
 mast cell leukemia: blood and lymphatic disease, immune system disease, neoplastic disease
 Leukemia, Mast-Cell (MeSH)

IT Diseases
 systemic mastocytosis: congenital disease, integumentary system disease

IT Chemicals & Biochemicals
 STI571: antineoplastic-drug, enzyme inhibitor-drug; c-kit: mutation; **stem cell factor [SCF]**; tyrosine kinase [EC 2.7.1.112]: regulation

IT Methods & Equipment
 short-term culture: culturing techniques, laboratory techniques

IT Miscellaneous Descriptors
 tumor growth regulation

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 HMC-1 cell line (cell line): human mast cell leukemia cells
 K562 cell line (cell line): human chronic myeloid leukemia cells
 human (common): adolescent, adult, aged, middle age, patient, female, male
 Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 152459-95-5 (STI571)
80449-02-1 (tyrosine kinase)
80449-02-1 (EC 2.7.1.112)

L121 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:483580 BIOSIS
DN PREV200100483580
TI The C-kit signaling pathways in normal and mastocytosis mast cells.
AU Chan, I. [Reprint author]; Kayashima, K. [Reprint author]; Ma, Y.;
Longley, B.; Tharp, M. [Reprint author]
CS Dermatology, Rush-Presbyterian-St-Luke's Medical Center, Chicago, IL, USA
SO Journal of Investigative Dermatology, (August, 2001) Vol. 117, No. 2, pp.
489. print.
Meeting Info.: 62nd Annual Meeting of the Society for Investigative
Dermatology. Washington, DC, USA. May 09-12, 2001.
CODEN: JIDEAE. ISSN: 0022-202X.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English
ED Entered STN: 17 Oct 2001
Last Updated on STN: 23 Feb 2002

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Cytology - Human 02508
Biochemistry studies - Proteins, peptides and amino acids 10064
Integumentary system - Physiology and biochemistry 18504
Integumentary system - Pathology 18506
Development and Embryology - Pathology 25503
Immunology - General and methods 34502

IT Major Concepts
Integumentary System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms
mast cell: immune system; skin: integumentary system

IT Diseases
mastocytosis: congenital disease, integumentary system disease
Mastocytosis (MeSH)

IT Chemicals & Biochemicals
C-kit: signaling pathways; C-kit receptor; JAK-3; Janus kinases; UO126;
WHI-P131; mitogen activated kinases; **stem cell
factor**

IT Miscellaneous Descriptors
Meeting Abstract

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
HMC-1 cell line: human mastocytosis cells
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 161384-16-3 (Janus kinases)
202475-60-3 (WHI-P131)

L121 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:320160 BIOSIS
DN PREV200100320160
TI Effects of the tyrosine-kinase inhibitor STI571 on mutated kit and
neoplastic mast cells.
AU Akin, Cem [Reprint author]; Longley, B. Jack; Brockow, Knut
[Reprint author]; Metcalfe, Dean D. [Reprint author]
CS Laboratory of Allergic Diseases, NIAID, NIH, Bethesda, MD, USA
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 747a. print.

Meeting Info.: 42nd Annual Meeting of the American Society of Hematology.
San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.

CODEN: BLOOAW. ISSN: 0006-4971.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LA English

ED Entered STN: 4 Jul 2001

Last Updated on STN: 19 Feb 2002

AB STI571 is a tyrosine kinase inhibitor which inhibits bcr-abl, and the kinase activity of the receptor for PDGF; and has been reported to inhibit **stem cell factor** receptor (KIT) and tumors bearing activating KIT mutations. It has been shown to have cytotoxic activity on chronic myeloid leukemia (CML) cells carrying bcr-abl and is currently under evaluation as a treatment for CML. Because activating mutations of c-kit affecting codon 816 are associated with most adult human mast cell neoplasms, we determined whether STI 571 exerted a similar cytotoxic effect on neoplastic human mast cells. We thus investigated the effect of addition of STI571 in increasing concentrations (0.01 to 10 micromolar) to bcr-abl positive (K562) and negative (U937) cells as well as the HMC-1 human mast cell leukemia cell line carrying two different activating c-kit mutations in codons 816 or 560. STI571 failed to inhibit the growth of U937 cells as well as HMC-1 cells bearing the 816 mutation but effectively suppressed the proliferation of K562 cells and HMC-1 expressing only the 560 mutation at concentrations greater than 0.1 micromolar. Consistent with these in vitro observations, STI571 inhibited ligand induced phosphorylation of transiently transfected wild type KIT in COS cells but failed to inhibit KIT activated by the 816 mutation in the same system. We then determined the effects of STI571 on mast cell numbers in bone marrow aspirates obtained from 7 patients with mastocytosis. The bone marrow mononuclear cell fractions containing the mast cells were incubated in increasing concentrations of STI571 for up to 8 days in serum-free medium in presence of **stem cell factor**. STI571 caused a dose-dependent reduction in total cell numbers as well as absolute mast cell numbers; however STI571 did not induce preferential killing of neoplastic mast cells under these culture conditions. These results suggest that STI571 does not significantly inhibit autophosphorylation of KIT carrying an activating codon 816 mutation at pharmacologic doses and is not preferentially cytotoxic to neoplastic human mast cells in short term cultures. Studies evaluating the effects of STI571 on long-term human mast cell cultures are currently underway.

CC Neoplasms - Therapeutic agents and therapy 24008
General biology - Symposia, transactions and proceedings 00520
Cytology - Human 02508
Genetics - General 03502
Genetics - Human 03508
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004

IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics);
Pharmacology; Tumor Biology

IT Chemicals & Biochemicals
STI 571: antineoplastic-drug, mutated KIT **stem cell factor** receptor effects, tyrosine kinase inhibitor

IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster

ORGN Classifier
Hominidae 86215
Super Taxa

Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name

HMC-1 cell line: drug treatment, human mast cell leukemia cell line,
in-vitro model system

Taxa Notes

Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 152459-95-5 (STI 571)

L121 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 2001:231346 BIOSIS

DN PREV200100231346

TI **SCF/c-kit** signaling is required for cyclic regeneration of the
hair pigmentation unit.

AU Botchkareva, Natalia V.; Khlgatian, Mary; Longley, B. Jack;
Botchkarev, Vladimir A.; Gilchrest, Barbara A. [Reprint author]

CS Department of Dermatology, Boston University School of Medicine, 609
Albany St., Boston, MA, 02118, USA
bgilchre@bu.edu

SO FASEB Journal, (March, 2001) Vol. 15, No. 3, pp. 645-658. print.
CODEN: FAJOEC. ISSN: 0892-6638.

DT Article

LA English

ED Entered STN: 16 May 2001

Last Updated on STN: 18 Feb 2002

AB Hair graying, an age-associated process of unknown etiology, is
characterized by a reduced number and activity of hair follicle (HF)
melanocytes. **Stem cell factor (SCF)**
) and its receptor c-kit are important for melanocyte survival during
development, and mutations in these genes result in unpigmented hairs.
Here we show that during cyclic HF regeneration in C57BL/6 mice,
proliferating, differentiating, and melanin-producing melanocytes express
c-kit, whereas presumptive melanocyte precursors do not. **SCF**
overexpression in HF epithelium significantly increases the number and
proliferative activity of melanocytes. During the induced hair cycle in
C57BL/6 mice, administration of anti-c-kit antibody dose-dependently
decreases hair pigmentation and leads to partially depigmented (gray) or
fully depigmented (white) hairs, associated with significant decreases in
melanocyte proliferation and differentiation, as determined by
immunostaining and confocal microscopy. However, in the next hair cycle,
the previously treated animal grow fully pigmented hairs with the normal
number and distribution of melanocytes. This suggests that melanocyte
stem cells are not dependent on **SCF/c-kit** and when appropriately
stimulated can generate melanogenically active melanocytes. Therefore,
the blockade of c-kit signaling offers a fully reversible model for hair
depigmentation, which might be used for the studies of hair pigmentation
disorders.

CC Biochemistry studies - General 10060

Biochemistry studies - Proteins, peptides and amino acids 10064

Integumentary system - Physiology and biochemistry 18504

IT Major Concepts

Biochemistry and Molecular Biophysics; Integumentary System (Chemical
Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms

hair: integumentary system, graying, pigmentation unit; pigmentation
unit, cyclic regeneration

IT Chemicals & Biochemicals

c-kit; **stem cell factor**

IT Miscellaneous Descriptors

signal transduction

ORGN Classifier

Muridae 86375

Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia

Organism Name

mouse: strain-C57BL/6

Taxa Notes

Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
Rodents, Vertebrates

L121 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2000:389499 BIOSIS
 DN PREV200000389499
 TI Indolinone derivatives inhibit constitutively activated KIT mutants and
 kill neoplastic mast cells.
 AU Ma, Yongsheng; Carter, Eric; Wang, Xiaomei; Shu, Chang; McMahon, Gerald;
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 SO Journal of Investigative Dermatology, (February, 2000) Vol. 114, No. 2,
 pp. 392-394. print.
 CODEN: JIDEAE. ISSN: 0022-202X.
 DT Article
 LA English
 ED Entered STN: 13 Sep 2000
 Last Updated on STN: 8 Jan 2002
 AB Mastocytosis is a neoplastic disease caused at least in part by somatic
 mutations of the c-KIT protooncogene resulting in constitutive activation
 of its protein product, KIT, the receptor tyrosine kinase for **stem**
cell factor. KIT stimulates mast cell proliferation and
 prevents apoptosis of neoplastic mast cells. To develop potential
 therapies for mastocytosis we used indolinones, small molecules that
 inhibit tyrosine kinases. Four indolinone derivatives (SU4984, SU6663,
 SU6577, and SU5614) inhibited wild-type KIT, but variably inhibited
 constitutively activated KIT mutants. SU4984, SU6577, and SU5614 were
 effective against KIT with juxtamembrane activating mutations, whereas
 only SU6577 could suppress KIT containing either juxtamembrane or kinase
 domain activating mutations. Furthermore, SU4984, SU6577, and SU5614
 killed neoplastic mast cells expressing a juxtamembrane-mutated KIT,
 whereas SU4984 and SU6577 killed neoplastic mast cells expressing KIT
 bearing a kinase domain mutation. These data show a direct correlation
 between inhibition of constitutively activated KIT and the death of
 neoplastic mast cells, and point to specific tyrosine kinase inhibitors as
 a potential therapy aimed directly at a cause of mastocytosis.
 CC Development and Embryology - Pathology 25503
 Cytology - Animal 02506
 Genetics - General 03502
 Genetics - Animal 03506
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Enzymes - General and comparative studies: coenzymes 10802
 Integumentary system - Physiology and biochemistry 18504
 Integumentary system - Pathology 18506
 Neoplasms - Immunology 24003
 Neoplasms - Pathology, clinical aspects and systemic effects 24004
 Immunology - General and methods 34502
 Immunology - Immunopathology, tissue immunology 34508
 IT Major Concepts
 Molecular Genetics (Biochemistry and Molecular Biophysics); Immune
 System (Chemical Coordination and Homeostasis); Integumentary System
 (Chemical Coordination and Homeostasis); Tumor Biology
 IT Diseases
 mastocytosis: congenital disease, integumentary system disease
 Mastocytosis (MeSH)
 IT Chemicals & Biochemicals
 indolinone derivatives; **stem cell factor**;
 tyrosine kinase; murine c-KIT gene: mutation

ORGN Classifier
 Muridae 86375
 Super Taxa
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 P815 cell line: neoplastic mast cells
 Taxa Notes
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
 Rodents, Vertebrates
 RN 80449-02-1 (tyrosine kinase)

=> d his

(FILE 'HOME' ENTERED AT 16:31:55 ON 12 AUG 2004)
 SET COST OFF

FILE 'HCAPLUS' ENTERED AT 16:32:04 ON 12 AUG 2004

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      E LONGLEY B/AU
L1      33 S E4-E6
L2      11 S E42
L3       7 S E37
L4       1 S E36
L5      52 S L1-L4
L6     414 S STEM CELL (L) FACTOR (L) SIGNAL? (L) PATHWAY
L7       3 S L5 AND L6
      E STEM CELL FACTOR/CT
L8     2301 S E3
      E E3+ALL
L9     1126 S E5,E6
L10    3427 S L8,L9
L11     20 S L10 (L) SIGNAL? PATHWAY
L12    208 S L10 AND SIGNAL? (L) PATHWAY?
L13    102 S L10 AND SIGNAL? PATHWAY?
L14    494 S L6,L11-L13
L15    2182 S L10 AND (PD<=19990506 OR PRD<=19990506 OR AD<=19990506)
      E CONTACT DERMATITIS/CT
      E E3+ALL
L16    3380 S E2
      E DERMATITIS/CT
L17    1494 S E5,E6,E12
      E E3+ALL
L18    11725 S E8+NT
L19    2277 S CONTACT DERMATITIS
L20     6 S L15 AND L16-L19
      E HYPERPIGMENTATION/CT
      E E3+ALL
L21    196 S E2
L22    570 S HYPERPIGMENT?
L23     8 S L15 AND L21,L22
      E ASTHMA/CT
L24    15205 S E3-E5
      E E3+ALL
L25    15205 S E9
      E E11+ALL
L26    8847 S E5,E6
L27    29150 S ?ASTHMA?
L28     15 S L15 AND L24-L27
      E SKIN INFLAMMATION/CT
      E E4+ALL
      E SKIN, DISEASE/CT
      E CUTANEOUS INFLAMMATION/CT
  
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      E SKIN DISEASE/CT
L29      1 S E4
      E E4+ALL
      E E2+ALL
L30      69482 S E6,E7,E5+NT
L31      37 S L15 AND L29,L30
L32      11 S L15 AND (SKIN OR DERM? OR EPIDERM? OR CUTAN?) (S)?INFLAM?
      E BRONCHOSPASM/CT
      E E3+ALL
L33      1 S L15 AND E2
L34      2 S L15 AND ?BRONCH?(L)?SPASM?
      E ANAPHYLAXIS/CT
L35      5 S L15 AND E3-E7
      E E3+ALL
L36      5 S L15 AND E3,E2+NT
L37      11 S L15 AND E16+OLD,NT
L38      49 S L15 AND E18+OLD,NT
L39      16 S L15 AND E19+OLD,NT
L40      0 S L15 AND E20+OLD,NT
      E MASTOCYTOSIS/CT
      E E3+ALL
L41      249 S E2
L42      356 S MASTOCYTOS?
L43      15 S L15 AND L41,L42
      E URTICARIA/CT
L44      1099 S E3+OLD,NT
L45      1885 S URTICAR?
L46      6 S L15 AND L44,L45
      E HYPERSENSITIVITY/CT
      E E3+ALL
L47      2 S L15 AND E2
L48      0 S L15 AND E6
L49      0 S L15 AND E8
L50      6 S L15 AND HYPERSENSITIV?
      E AIRWAY INFLAMMATION/CT
      E E3+ALL
L51      0 S L15 AND E2
      E RESPIRATORY TRACT, DISEASE/CT
L52      57 S L15 AND E3+OLD,NT
      E INTERSTITIAL CYSTITIS/CT
      E CYSTITIS/CT
L53      0 S L15 AND E3
      E E3+ALL
L54      0 S L15 AND E2
L55      0 S L15 AND INTERSTIT? CYSTIT?
L56      928 S L15 AND KIT
L57      177 S L56 AND (?TUMOR? OR ?NEOPLAS? OR ?MALIGN? OR ?CANCER? OR ?MET
      E CONTRACEPTION/CT
      E E7+ALL
L58      5 S L15 AND E5
      E E7+ALL
L59      53 S L15 AND E3+NT
L60      350 S L20,L23,L28,L31-L39,L43,L46,L47,L50,L52,L57-L59
L61      70 S L60 AND SIGNAL?
L62      25 S L61 AND PATHWAY
L63      24 S L60 AND L14
L64      25 S L62,L63
L65      25 S L7,L64
L66      6 S L65 AND (SKIN OR EPIDERM? OR DERM? OR CUTAN? OR SUBCUTAN?)
L67      3 S L66 AND L5
L68      19 S L65 NOT L66
      SEL DN AN 1 12 13
L69      3 S E1-E9

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L70 6 S L67,L69
 E SIGNAL/CT
 E E40+ALL
 L71 111592 S E1
 E E11+ALL
 L72 309686 S E4+NT
 L73 37 S L60 AND L71,L72
 L74 21 S L73 NOT L65
 SEL DN AN 4 5
 L75 2 S E1-E6
 SEL DN AN 21 L74
 L76 1 S E7-E9
 L77 9 S L70,L75,L76 AND L1-L76
 L78 9 S L77 AND (SCF OR STEM CELL FACTOR)

FILE 'HCAPLUS' ENTERED AT 17:02:34 ON 12 AUG 2004

FILE 'WPIX' ENTERED AT 17:03:59 ON 12 AUG 2004

L79 1228 S (STEM CELL FACTOR OR SCF)/BIX
 L80 3 S L79 AND CONTACT DERMATITIS/BIX
 L81 122 S (B04-H16 OR C04-H16)/MC
 L82 1 S L81 AND CONTACT DERMATITIS/BIX
 L83 77 S L79,L81 AND (B14-N17? OR C14-N17? OR B12-A07 OR C12-A07)/MC
 L84 24 S L79,L81 AND (B14-N17C OR C14-N17C)/MC
 L85 24 S L80,L82,L84
 E LONGLEY/AU
 L86 3 S E7
 L87 1 S L86 AND L79,L81
 L88 2 S L86 NOT L87
 L89 3 S L80,L82,L87
 L90 3 S (B04-M01 OR C04-M01)/MC AND L85
 L91 1 S L90 NOT JAMM
 L92 6 S L85 AND SIGNAL?/BIX
 L93 3 S L89 AND L79-L92

FILE 'WPIX' ENTERED AT 17:14:46 ON 12 AUG 2004

FILE 'DPCI' ENTERED AT 17:14:58 ON 12 AUG 2004

 E LONGLEY/AU
 L94 2 S E7

FILE 'DPCI' ENTERED AT 17:15:35 ON 12 AUG 2004

FILE 'MEDLINE' ENTERED AT 17:16:08 ON 12 AUG 2004

 E STEM CELL FACTOR/CT
 E E3+ALL
 L95 2592 S E30
 L96 1793 S L95 AND PY<=1999
 E CONTACT DERMATITIS/CT
 E E3+ALL
 L97 0 S L96 AND E2+NT
 L98 0 S L96 AND CONTACT DERMATITIS
 E DERMATITIS/CT
 E E3+ALL
 L99 56 S L96 AND E3+NT
 L100 0 S L99 AND E4+NT
 E HYPERPIGMENTATION/CT
 E ASTHMA/CT
 E SKIN INFLAMMATION/CT
 E INFLAMMATION/CT
 E BRONCHOSPASM/CT
 E E3+ALL
 E ANAPHYLAXIS/CT

E MASTOCYTOSIS/CT
E URTICARIA/CT
E HYPERSENSITIVITY/CT
E AIRWAY INFLAMMATION/CT
E RESPIRATORY/CT
E RESPIRATORY DISEASE/CT
E RESPIRATORY TRACT DISEASE/CT
L101 49 S L96 AND (HYPERPIGMENTATION+NT OR ASTHMA+NT OR ANAPHYLAXIS+NT
E BRONCHOSPASM/CT
E E3+ALL
L102 0 S L96 AND E2+NT
E INTERSTITIAL CYSTITIS/CT
E E3+ALL
L103 1 S L96 AND E2+NT
L104 374 S L96 AND C4./CT
L105 402 S L99,L101,L104
L106 67 S L105 AND SIGNAL?
L107 27 S L106 AND PATHWAY?
E SIGNAL/CT
E E19+ALL
L108 27 S E2+NT AND L106
L109 27 S E2+NT AND L105
L110 40 S L107-L109
L111 2 S STEM CELL FACTOR(L)AI/CT AND L110
L112 12 S L110 AND INHIBIT?
L113 7 S L112 AND L95/MAJ
L114 2 S L111 AND L113

FILE 'MEDLINE' ENTERED AT 17:26:21 ON 12 AUG 2004

FILE 'BIOSIS' ENTERED AT 17:26:27 ON 12 AUG 2004
E LONGLEY/AU

L115 44 S E8-E12
L116 14 S L115 AND (SCF OR STEM CELL FACTOR)
L117 30 S L115 NOT L116
L118 26 S L115 AND PY<=1999
L119 7 S L118 AND L116
L120 19 S L118 NOT L119

FILE 'BIOSIS' ENTERED AT 17:28:38 ON 12 AUG 2004

L121 7 S L116 NOT L119

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